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SPIDER POISONING

EXPERIMENTAL STUDY OF THE EFFECTS OF THE BITE OF THE FEMALE LATRODECTUS MACTANS IN MAN

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The belief that the bite [1] of the spider Latrodectus mactans,[2] common in the southern half of the United States (fig. 1), is poisonous for man has been recognized for centuries.[3] Evidence for the truth of this belief has rested largely on the statement of patients that immediately prior to the onset of their symptoms they had been bitten by a spider answering the description of Latrodectus mactans.[4] In other cases, the spider alleged to have been responsible for the bite was caught and identified as a member of this species by competent arachnologists. Many physicians accepted this evidence of their patients and reported cases of spider poisoning in the scientific literature.

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1. Strictly speaking this spider does not "bite" at any time. It pierces the integument of its victim by means of a pair of extremely sharp, chitinous claws (fig. 3) articulating on the basal segments of the chelicerae. The chelicerae are considered as modified antennae and constitute the first pair of appendages. They lie in front of and are attached above the mouth parts. Near the tip of each claw is a small orifice through which the venom from the poison gland is discharged in the wound. The mouth parts are used only in pressing and sucking the fluid contents of the victim.

2. This species possesses many scientific synonymous names (Petrunkevitch, Alexander: A Synonymic Index-Catalogue of Spiders of North, Central and South America with All Adjacent Islands, Bull. Am. Mus. Nat. History **29**:180 [May] 1911) and nicknames (Bogen [5a]). Of the former, that most commonly used is "Latrodectus mactans"; of the latter, "black widow." References in the literature are all in connection with the female of the species. Little attention is given the male though it appears that it also possesses poisonous properties.

3. (*a*) Merriam, C. Hart: The Dawn of the World, Myths and Weird Tales Told by the Mewan Indians of California, 1910; quoted by Comstock, J. H.: The Spider Book, New York, Doubleday, Page & Company, 1913, p. 359. (*b*) Robie, T.: An Instance of the Venom of Spiders, Phil. Tr. Roy. Soc. London **6**:52, 1726; On the Effects of Inoculation; the . . . ; and the Venom of Spiders, Phil. Tr. Roy. Soc. London **7**:20, 1724; quoted by Bogen.[5c]

4. Dorsal and ventral views of the adult female Latrodectus mactans are shown in the article on the "Life History of Latrodectus Mactans" in this issue (figs. 1 *G* and *H*), p. 844.

Bogen,[5] in a comprehensive review of the literature on this subject, has collected nearly four hundred cases of this kind, ranging from the year 1720 [3b] to 1931. Twelve cases in which a fatal outcome was attributed to the bite of this spider are included. Many other cases, as personal communications from local physicians testify, are never published, and, consequently, those reported represent but a small fraction of the actual number which have occurred. Since 1931 several authors [6] have reported additional cases.

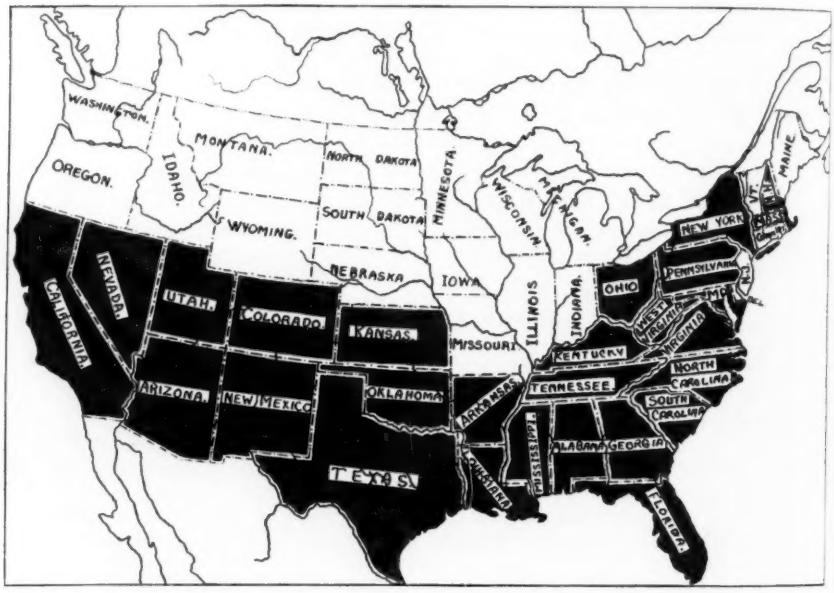

Fig. 1.—Distribution of Latrodectus mactans in the United States. The states in black are those in which, according to Bogen,[5c] this spider has been found or from which bites have been reported.

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5. (*a*) Bogen, Emil: Arachnidism: Spider Poisoning, Arch. Int. Med. **38**: 623 (Nov.) 1926 (an excellent bibliography is given in the reprints); (*b*) Arachnidism: A Study in Spider Poisoning, J. A. M. A. **86**:1894 (June 19) 1926; (*c*) Poisonous Spider Bites, Ann. Int. Med. **6**:375 (Sept.) 1932 (note the additional bibliography on spider poisoning).

6. Combs, J. J.: Spider Poisoning, South. Med. & Surg. **94**:442 (July) 1932. Morton, C. B.: Acute Abdominal Symptoms in Arachnidism, Arch. Surg. **26**:64 (Jan.) 1933. Tolleson, H. M.: Arachnoidism, J. M. A. Georgia **22**:30 (Jan.) 1933. Walker, W. A.: Arachnoidism, J. M. A. Georgia **22**:105 (March) 1933. Noland, L.: Arachnidism, Am. J. Surg. **20**:758 (June) 1933. Walsh, G., and Morgan, W. G.: Arachnidism, Am. J. M. Sc. **186**:413 (Sept.) 1933. Abrams, M. J.: Arachnidism, Bull. School Med. Univ. Maryland **18**:92 (Jan.) 1934.

This evidence, coupled with similar reports on the poisonous properties of the several closely related species distributed around the world (fig. 2), is strongly suggestive of the poisonous nature of this spider. Irrespective, however, of the integrity and intelligence of the patients thus bitten, such evidence remains essentially circumstantial in nature. As such, it affords some basis for the skepticism, so abundantly displayed

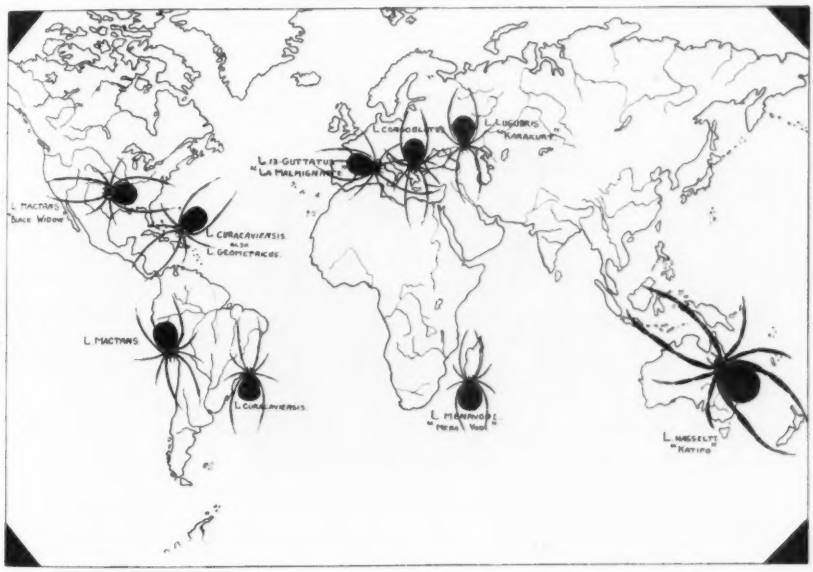

Fig. 2.—World distribution of genus Latrodectus. As this is based on the literature of Latrodectus poisoning, no attempt at absolute geographic exactitude in the distribution of each species has been made. Spiders of this genus are universally feared for the poisonous effects of their bite. The uncommon prevalence of local nicknames for these spiders is of interest.

in the literature,[7] that so small and timid a creature could be capable of producing such severe general symptoms in man.

7. Van Hasselt, A. W. M.: Het spinnenvergift, Nederl. tijdschr. v. geneesk. **18**:57, 1882. Emerton, J. H.: Common Spiders of the United States, Boston, Ginn and Company, 1902, p. 124. Bogen.[5a]

Further grounds for skepticism on the part of those who have had no intimate acquaintance with the effect of the bite of this spider are afforded in the conflicting results of experimental studies in animals and in man. Thus, Marx [8] reported no effect in a guinea-pig following the bite of a mature female Latrodectus mactans. Escomel,[9] on the contrary, reported marked symptoms, while Houssay [10] and Troise [11] reported severe symptoms followed by death in many cases. Baerg [12] reported "moderately pronounced" symptoms in two rats in a series of four following the spider's bite, while Bogen [13] reported marked symptoms with a high mortality in mice and in rats. Experimental

Fig. 3.—Adult female Latrodectus mactans dissected to show the two poison glands lying in the cephalothorax. The two chelicerae,[1] with their sharp, chitinous claws directed medially, are seen anteriorly lying between the palpi (× 10).

8. Marx, George: On the Effect of the Poison of Latrodectus Mactans Walck. Upon Warm-Blooded Animals, Proc. Entomol. Soc. **1**:85 (Oct. 2) 1890.

9. Escomel, E.: Poisonous Spiders, Rev. Asoc. méd. argent. **27**:853 (Dec.) 1917; quoted by Kellaway, C. H.: Venom of Latrodectus hasseltii, M. J. Australia **1**:41 (Jan. 11) 1930.

10. Houssay, B. A.: Arañas Venenosas, Conf. Soc. sud.-am. de hyg., Buenos Aires **1**:545, 1917; quoted by Troise.[11]

11. Troise, E.: Estudio farmacológico sobre la ponzoña del "Latrodectus mactans," Rev. Soc. argent. de biol. **4**:447, 1928; abstr., Action pharmacodynamique du venin de Latrodectus mactans, Compt. rend. Soc. de biol. **99**:1431 (Nov. 9) 1928.

12. Baerg, W. J.: Effects of the Bite of Latrodectus Mactans Fabr., J. Parasitol. **9**:161 (March) 1923.

13. Bogen.[8a,c]

studies [14] show marked reactions in mice, rats, guinea-pigs and chickens. In mice the mortality was practically 100 per cent. Rabbits, cats dogs and sheep seemed little affected. Experimental results with transplants and the injection of extracts of the poison gland (fig. 3) are likewise confusing and inconclusive.

Direct experimental evidence that the bite of Latrodectus mactans may be poisonous for man is furnished by the work of Baerg.[12] On July 9, 1922, he placed one of these spiders on his little finger but could not induce it to bite. A further attempt with a second spider resulted in a bite, but the subsequent effect was local, mild and transitory. The following day the first spider was again placed on the finger and permitted to bite for five seconds. On this occasion severe aching pains in the muscles of the lumbar region, shoulders, chest and legs appeared, but Baerg concluded that the sharp pain in the finger and hand was the most prominent feature. The negative results of the first two attempts, however, together with the negative results of Lucas,[15] Simon [16] and Bordas [17] following bites by Latrodectus, have in some measure detracted from the conclusiveness of his experiment. Bordas reported being repeatedly bitten on the hand by Latrodectus tredecimguttatus Rossi with no evidence of systemic poisoning. The Latrodectus tredecimguttatus, commonly known as "la malmignatte," is found in southern Europe (fig. 2) where it is regarded as poisonous to man, much as is the Latrodectus mactans in this country. Closely related though these species undoubtedly are, it is, nevertheless, hazardous to assume that experimental results with the European "malmignatte" would be equally applicable to the American "black widow." [2] Yet this assumption has, by inference, not infrequently been made.[18]

In a series of excellent articles Bogen [5] has revived the interest of the medical profession of this country in the severe systemic symptoms resulting from the bite of Latrodectus mactans. Since experimental results in support of such a clinical entity have not been considered conclusive, an experimental study of the effects of the bite of this spider in animals and man has been made. The results in man, herewith submitted, emphatically support the contention of Bogen that arachnidism (spider poisoning) may be considered "a true clinical entity in the field of general medicine."

14. Blair, A. W.: Effects of the Bite of the Female Latrodectus mactans in Animals, to be published.

15. Lucas, M.: Ann. Entomol. Soc. de France, 1843, p. 8; quoted by Bordas.[17] Bogen.[5a]

16. Simon, E.: Histoire naturelle des araignées, Paris, 1882-1903; quoted by Bordas.[17]

17. Bordas, L.: Recherches sur l'effet des piqûres du Latrodectus 13-guttatus Rossi ou Malmignatte, Compt. rend. Acad. d. sc. **133**:953 (Dec. 2) 1901.

18. Berland, Lucien: Le venin des Araignées, Rev. sc. **65**:267 (May 14) 1927.

EXPERIMENTAL BITE IN MAN

The subject of the experiment, begun on Nov. 12, 1933, was a man (myself), aged 32, weighing 168 pounds (76.2 Kg.), athletically inclined and in excellent health. The normal clinical findings in health had been recorded daily for one week prior to the bite. Reaction to bee stings and mosquito bites was normal.

The spider (no. 111.33) selected for the experiment, a mature female Latrodectus mactans,[4] was found in a rock pile near my residence on October 25. Since then it had been kept in a jar in the laboratory. It was fed last (water beetle) on October 29. On the day of the experiment it was of moderate size, active and glossy black, with characteristic adult markings, and appeared to be in excellent condition.

10:45 a. m.: With a pair of splinter forceps, the spider was gently grasped by the globose abdomen and applied to the medial surface of the terminal phalanx of the little finger of the left hand. The spider bit the moment it came into contact with the skin surface, twisting the cephalothorax from side to side as though to sink the claws of the chelicerae deeper into the flesh. The sensation resembled that of the prick of a very sharp needle, accompanied, however, by a burning sensation which increased in intensity during the biting period. The spider was permitted to bite for ten seconds. On its removal a small drop of a clear, whitish fluid, slightly streaked with brown, was observed at the site of the bite. This was allowed to remain untouched for one minute and was then wiped off with a cotton pledget. No definite marks of skin puncture were seen with the naked eye or with low magnification.

First Stage; Lymphatic Absorption.—10:47 a. m.: A bluish, pinpoint mark was seen at the site of the bite, surrounded by an area of blanching, 4 mm. in diameter; a hot, burning sensation was present in the finger.

10:52 a. m.: The area of blanching was more marked; the entire terminal phalanx was reddened; there was a throbbing, lancinating pain in the bitten finger.

11:00 a. m.: Dull, aching pain was noted between the fourth and fifth metacarpophalangeal joints of the left hand with a slight numbness along the ulnar side of the hand; beads of perspiration were present at the site of the bite.

11:02 a. m.: Dull, aching pain was present on the inner surface of the upper arm in the region of the superficial cubital gland (tenderness of this gland was still present two weeks after the bite); the terminal phalanx of the bitten finger was dark purplish red, slightly swollen and very painful.

11:05 a. m.: Dull, aching pain was present in the left axilla; the whole arm had a dull, aching, slightly numb feeling.

11:07 a. m.: Slight, aching pain was present over the lateral surface of the left side of the chest; pains in the axillary region now commanded more notice than the throbbing, occasionally lancinating pain in the finger.

11:18 a. m.: Slight, aching pains were present over the precordium.

Second Stage; Vascular Dissemination.—11:35 a. m.: The blood pressure was 106 systolic and 78 diastolic; the pulse rate was 75 and weaker than normal; the respiratory rate was 16, and respiration appeared to be slightly deeper than normal; there was a dull, drowsy, lethargic feeling. This was the first circulatory (general) effect noted.

11:50 a. m.: Slight, transient aching pains were noted in the epigastrium; there was a flushed, headachy feeling; the white cell count was 8,400, with 54 polymorphonuclears, 39 lymphocytes, 6 monocytes and 1 per cent eosinophils.

11:55 a. m.: Definite, aching pains were present in the epigastrium.

12:00 a. m.: Aching pains were present in the muscles of the neck; there was a feeling of general malaise; the blood pressure was 108 systolic and 82 diastolic; the pulse was weak, and its rate was 62.

(From this stage on notes were taken by assistants.)

12:10 p. m.: Aching pains were present over the whole abdomen; the latter was tense; there was a flushed, trembly feeling in the legs.

(At this time the subject was driven 3 miles to the hospital. During the fifteen minutes thus taken the abdominal pains became rapidly more severe.)

12:30 p. m.: Severe, aching pain was present in the lumbar region, abdomen and chest, with a feeling of constriction in the latter; speech was difficult and jerky; respirations were rapid and labored, with a sharp brisk expiration accompanied by an audible grunt; the abdomen was rigid; the heart sounds were slow, regular and normal in character; the pulse was weak and thready; its rate was 60.

(At this time two electrocardiograms were made. These were found to be normal, differing in no essential from that taken several days prior to the experiment.)

12:37 p. m.: There were agonizing pains in the lumbar region, abdomen and chest; the abdomen was rigid, boardlike, with some tenderness in the epigastric region; the patient stated that it was torture to lie still on his back while the electrocardiograms were being made.

12:45 p. m.: The pains had spread to the legs; the patient lay on his right side with the legs, arms and body flexed; the respirations were labored, with a gasping inspiration and a sharp, jerky expiration accompanied by an uncontrollable, loud, groaning grunt.

12:50 p. m.: The patient was unable to straighten up or stand, showing almost rigid flexion of the legs, tremor, extreme ashy pallor and cold clammy sweat, with the general appearance of being in a condition of profound shock; he was undressed and placed in a hot bath; he stated that he experienced an immediate, appreciable diminution of pain and a sense of general relief. The bitten finger was swollen, cyanotic, tender and painful.

1:04 p. m.: The pain, though partially relieved, was still severe; the respirations were still labored; spasm of the flexor muscles of the forearms and adductors of the thumbs ("accoucheur's hand") was present; a tingling sensation was felt in the hands and feet; the blood pressure was 75 systolic (no auscultatory diastolic reading was obtainable); the pulse was rapid, uncountable, weak and thready.

1:15 p. m.: The lips were tense and contracted, causing the mouth to assume an oval shape; the patient complained of slight dizziness and throbbing in the head.

(Note by Dr. J. M. Forney:[19] "I saw the patient first at about 1:15 p. m. I found him in excruciating pain, gasping for breath and reclining in a tub of very warm water. I do not recall having seen more abject pain manifested in any other medical or surgical condition. All the evidences of profound medical shock were present.")

1:30 p. m.: The patient was removed from the bath and placed in bed; the face and body were very red; the respirations were still labored but definitely easier than prior to the bath.

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19. Dr. J. M. Forney gave personal and professional aid during this experiment. Figure 3 is a reproduction of a photograph by G. G. Goldenberg. R. O. Griffith and E. S. Porter gave valuable assistance.

1:45 p. m.: The respirations had become increasingly labored and the pains more severe since removal from the bath; the patient writhed about on the bed; hot water bottles were placed to the abdomen and back, giving some relief from pain.

1:52 p. m.: The patient was perspiring profusely; the respirations were less labored; the blood pressure was 80 systolic and 50 diastolic, the pulse was weak; its rate was 120.

Third Stage; Elimination.—2:05 p. m.: The patient stated that he felt a little better; he was given ¼ grain (0.16 Gm.) of morphine hypodermically.

3:40 p. m.: The white cell count was 13,200 with 79 polymorphonuclears, 19.5 lymphocytes and 1.5 per cent monocytes.

4:05 p. m.: The patient vomited.

5:25 p. m.: A red streak extending up the back of the left hand from between the fourth and fifth metacarpophalangeal joints was noted.

7:45 p. m.: The patient was very restless; he still complained of severe pain in the abdomen, lumbar region and legs and of sharp intermittent pains in the bitten finger; he drank copiously and perspired freely; the eyes were red and watery and the face appeared swollen; the abdomen was still rigid; the blood pressure was 154 systolic and 92 diastolic; the pulse was stronger; its rate was 78; the respirations were shallow and still somewhat labored; the white cell count was 18,200 with 82 polymorphonuclears, 13 lymphocytes and 5 per cent monocytes.

November 13: The temperature which was normal at the commencement of the experiment became from 1 to 2 degrees subnormal during the period of shock. On the afternoon of November 12 and during the night of November 12 and 13 it rose 1 to 2 degrees above normal. It had returned to normal by the morning of November 13 and remained so thereafter.

The blood pressure reached its height the night of November 12. From that point it gradually fell, regaining normal limits by November 19.

6:30 a. m.: The patient was given a dose of magnesium sulphate.

8:15 a. m.: The patient stated that he spent a restless, sleepless, miserable night, perspiring freely and troubled by muscular pains and chilly sensations. Two tablets of a barbital derivative with amidopyrine gave no relief. Several hot baths were given for relief of pain. On one occasion the patient stated that he became so upset mentally that he was afraid if firm control was not exercised he would go insane. Following this ¼ grain of morphine was given hypodermically.

In the morning the patient complained of severe pains in the lumbar region and legs; the face had a swollen, puffy appearance; the eyes were red and watery; the abdomen was tense with slight epigastric tenderness.

9:30 a. m.: The urine showed a trace of albumin, a few pus cells, many red blood cells, epithelial cells and 25 blood and 5 granular casts under low power magnification. The white cell count was 19,150 with 77 polymorphonuclears, 18 lymphocytes and 5 per cent monocytes.

(The polymorphonuclear leukocytes had returned to normal by November 15. No significant variations were noted in the erythrocyte counts or hemoglobin content. Unfortunately no counts were made during the stage of shock and no chemical studies were made on the blood.)

4:10 p. m.: The patient complained of pains in the back and legs, and of weakness and chilliness; the face was flushed and swollen; the tongue was heavily furred, and the breath was foul; the abdomen was tense; tremor of the hands and a papular eruption on the inner surface of the bitten finger and along the ulnar side of the hand were present; the patient had passed several liquid stools.

8:00 p. m.: The patient's condition was much improved; rheumatoid pains in the legs were now the chief complaint; he had drunk large quantities of orange juice all day and perspired freely.

November 14, 8:00 a. m.: The patient stated that he passed a very restless night; he ate toast and grapefruit for breakfast.

Fig. 4.—Clinical chart depicting the variations in blood pressure and in pulse and respiratory rate recorded during this experiment. The onset and duration of the three stages as observed in this case are depicted.

12:00 a. m.: He stated that he was feeling much better; the chief complaints were rheumatoid pains in the legs and feet, chilliness, sweating and weakness; the face was less swollen, but the abdomen was still tense.

2:00 p. m.: The patient walked to the bathroom unaided; the urine showed a trace of albumin, many pus cells, a few red blood cells and a few granular casts under low power magnification.

(The urinary output was greatly reduced for the first five days following the bite. The effect on the urinary output of the abnormal loss of fluid through intestinal and cutaneous elimination during this period must not, however, be disregarded. The urinary output had returned to normal by November 18, coinciding with the cessation of excessive sweating.)

November 15, 8:00 a. m.: The patient stated that he slept at intervals during the night; the appetite was returning; rheumatoid pains in the legs and feet, chilliness and sweating of the legs and feet were the chief complaints; the abdomen was no longer tense and the face no longer swollen; the urine showed no albumin, few red blood cells, leukocytes, epithelial cells and numerous hyaline, granular and leukocytic casts.

11:00 a. m.: The patient was removed to his home by ambulance; he spent the remainder of the day in bed.

Final Progress Note.—From that time on recovery was rapid. The pain in the bitten finger had disappeared by the evening of the second day following the bite. A small, slightly tender, red papule was present at the site of the bite for two weeks, then disappeared. The rheumatoid pains in the legs and feet had disappeared by November 20. Slight edema of the ankles was noted the first few days on moving about. Urinalyses became normal on November 18. Generalized pruritus was present for some time, and desquamation of the hands and feet continued for about three weeks. All the signs and symptoms had, however, disappeared by November 20. Subsequently the health of the patient has been excellent. No sequelae have been noted to date (February 15, 1934).

COMMENT

A study of the clinical picture in this case indicates three well defined stages in its development. Lymphatic absorption of the injected venom, as evidenced by the proximal progress of pain along the lines of lymphatic drainage, constitutes the first stage. It is characterized by pains in the bitten finger and in the arm and by the absence of general systemic effects.

Passing through the axillary lymph glands, the venom reaches the blood stream via the efferent axillary lymph channels, the subclavian lymphatic trunk and the subclavian vein. This ushers in, secondly, the stage of vascular dissemination which is characterized, clinically, by the explosive onset of widespread agonizing muscular pains and a condition of profound shock. This was, in this case, the most painful and critical stage, and yet no mention of a period of shock in this condition has so far been encountered in the literature. Two possibilities may account for this discrepancy. 1. All persons bitten may not receive a quantity of venom sufficient to induce the degree of shock obtained in this case. 2. The patient may have recovered from the condition of shock before coming under medical observation.

The third stage, that of elimination of the venom or its toxic products, commences with the rapid recovery from shock. It is characterized, clinically, by hypertension, diaphoresis, gradually diminished muscular pain, a slight rise of temperature, polymorphonuclear leukocytosis and urinary evidence of renal damage. This clinical picture, coupled with the slight headache and edema of the face and ankles, is very suggestive of the development at this stage of an acute (toxic) nephritis. The damage to the kidneys probably results from the attempted elimination of the venom or its toxic products by that route.

The condition of shock, characteristic of the second stage, suggests the possibility of the presence of a histamine-like ingredient in the venom of the spider Latrodectus mactans. Such a possibility is further suggested by the secretagogue action (salivation and lacrimation), evidence of contraction of the bronchial and intestinal musculature and symptoms of acute prostration and collapse which have been noted [20] in certain animals bitten by this spider. It is of interest that certain histamine-like properties of another secretion, crotalin (rattlesnake venom), have been observed experimentally.[21]

The question as to whether the agonizing muscular pains may play a part in the production of shock must also be considered. It is noteworthy, however, that the blood pressure had commenced to fall prior to the development of the acute muscular pains.

Although the mortality rate in this condition is low, I believe, as a result of my experience, that the possibility of a fatal outcome should by no means be disregarded. The second stage is to be regarded as the most critical, particularly in persons with conditions such as diabetes, chronic cardiac disease, alcoholism or renal disease, which predispose to shock.

The development in man during convalescence of any degree of immunity to the venom of this spider remains unproved. I was presented with the opportunity of deciding this point, but lacked the courage to submit myself to a possible repetition of the first experience. Degrees of immunity to the bite of this spider can be developed in animals [22] and, on the assumption that man reacts likewise, convalescent serum has been used therapeutically. The results [5e] so far obtained are, however, inconclusive.

Lacking the history of a spider bite, or an acquaintance with the clinical picture which it may produce, one might well be excused for mistaking the symptoms for one of several acute conditions. Thus a perforated peptic ulcer, acute pancreatitis, ruptured ectopic pregnancy,

20. Troise.[11] Blair.[14]

21. Essex, H. E., and Markowitz, J.: A Comparison of the Physiologic Action of Crotalin and Histamine, Am. J. Physiol. **92**:705 (April) 1930.

22. Baerg.[12] Blair.[14].

tabetic crisis, ruptured appendix with generalized peritonitis and renal or biliary colic may be considered in arriving at a diagnosis. Similarity between the clinical picture presented in poisoning by this spider and perforated peptic ulcer, particularly, has subjected the patient, on more than one occasion, to the added risk of surgical intervention.[23]

TREATMENT

Rational therapeutic measures in combating the effects of the venom injected by the bite of Latrodectus mactans should recognize the following points: 1. The reaction is due to the instantaneous injection, through a very minute skin puncture, of small quantities of venom, followed by rapid lymphatic absorption. 2. The subsequent vascular dissemination of the venom throughout the body may result in the development of a condition of shock. 3. Recovery involves the neutralization or elimination of the injected venom. 4. The development of an acute nephritis in the later stages is indicated.

The minute skin punctures, the rapid absorption and the small amount of venom capable of producing such a severe reaction in man make it unlikely that local applications can exert any appreciable neutralizing effect on the injected venom. A sharp "X" incision through the site of the bite, if made in the first few minutes after the accident, probably offers the best possibility for an early elimination of the venom.

Treatment of the shock as seen in the second stage of this condition involves the use of the accepted means for counteraction. Thus, the adoption of measures tending to a restoration of capillary tone and blood volume are indicated, while the use of cardiac stimulants is contraindicated. The use of large doses of alcohol for the relief of pain is to be condemned, in view of its tendency to accentuate and prolong the much more serious condition of shock. For the same reason, morphine, in the notoriously high dosages found necessary for relief of the associated agonizing muscular pains, should, at this stage, be used with caution. In my case immersion in a hot bath gave immediate and marked relief from pain. It may be merely a happy coincidence that it also marked the termination of the period of shock and the initiation of a progressive general improvement. Baerg [12] also remarked on the relief given by frequent hot baths, and it is said that in Russia baths are used extensively in the treatment of the bite of the closely allied species, the "Karakurt," found in that country.

In view of the clinical indications of the development of an acute nephritis, treatment during the third stage should be directed to giving

23. Carrington, G. L.: Bilateral Diaphragmatic Pleurisy Simulating Perforated Gastric Ulcer, J. A. M. A. **88**:1395 (April 30) 1927. Bogen.[5e]

rest to the kidneys. On the assumption that the damage to the kidney arises during the elimination of the venom or its toxic products, the adoption of measures tending to aid in their possible elimination by other routes is indicated. The patient should be placed in a warm, well ventilated room, between woolen blankets and surrounded by hot water bottles. Frequent hot baths should be given. An intake of fluid sufficient to satisfy the patient's thirst should be encouraged, but in view of the damage to the kidneys fluids should not be forced. For the relief of pain and to secure rest, morphine may, at this stage, be used even in fairly high dosage. Spinal puncture is said to give considerable relief in many cases.[5e]

The use of specific antivenins and convalescent serum in this condition must await the collection of further clinical and experimental data before the therapeutic value of these agents can be safely estimated.

CONCLUSIONS

1. The venom injected by the bite of the adult female spider, Latrodectus mactans, is dangerously poisonous for man.

2. The development of the ensuing clinical picture may be divided into three stages, of which the second, that of shock, is the most critical.

3. The sequence of symptoms following the injection of venom by Latrodectus mactans is sufficiently characteristic to entitle it to recognition as a clinical entity in the field of general medicine.

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LIFE HISTORY OF LATRODECTUS MACTANS

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In spite of the clinical importance of the bite of the Latrodectus mactans no complete study of its life history has so far been made. In view of this fact and since it is the only spider found in this country the bite of which has definitely been proved capable of causing severe [1] and, in some cases, fatal [2] systemic reactions in man, observations on its life history are of interest. The observations presented are based on a two year study of this spider as found in the vicinity of Tuscaloosa, Ala. It includes observations of the spider both in its natural environment and as raised in captivity.

APPEARANCE

The full grown female Latrodectus mactans (fig. 1, *G* and *H*) has a large, globose abdomen attached by a slender pedicle to the much smaller cephalothorax. The body of an average-sized adult female is ½ inch (1.27 cm.) in length. The abdomen is ⅜ inch (0.95 cm.) in length and practically the same in width in the posterior third. When distended with food or eggs it overhangs the cephalothorax. The cephalothorax is ⅛ inch (0.32 cm.) in length and approximately the same in width at its broadest point. The slender, pointed legs when fully extended have a span of from 1½ to 2 inches (3.81 to 5.08 cm.). Laterally, they have a spread of 1½ to 1¾ inches (3.81 to 4.45 cm.).

The legs and body are a glossy black and as seen under the microscope are covered with short black hairs. On the ventral surface of the abdomen there is a rich red marking (fig. 1 *H*) consisting of a rectangular bar from the center of which rises an inverted triangle. It is shaped somewhat like an hour-glass and stands out in striking contrast to the surrounding black. Dorsal to the spinnerets in the midline of the convex surface of the abdomen is an additional red marking (fig. 1 *H*). These two markings constantly seen on the otherwise shiny black body are characteristic of the adult female and readily serve to distinguish this from other species of spiders. In immature females a broken row

From the Department of Pathology and Bacteriology, School of Medicine, University of Alabama.

1. Baerg, W. J.: Effect of Bite of Latrodectus mactans (Fabricius), J. Parasitol. **9**:161 (March) 1923. Blair, A. W.: This issue, p. 831.

2. Bogen, Emil: Arachnidism, A Study in Spider Poisoning, J. A. M. A. **86**:1894 (June 19) 1926; Arachnidism, Arch. Int. Med. **38**:623 (Nov.) 1926: Poisonous Spider Bites, Ann. Int. Med. **6**:375 (Sept.) 1932.

of red spots up the midline of the back is a constant finding. With the exception of the one above the spinnerets these gradually become suffused with black pigment and eventually disappear, though traces of them may remain in an apparently full grown female (fig. 1 *F*).

HABITAT

The species Latrodectus mactans is found in North, Central and South America from New Hampshire south through Central America and along the west coast of South America to Tierra del Fuego. Of particular interest, however, is its widespread distribution throughout the southern half of the United States. It is very common throughout central Alabama. In this region the spiders are found in the angles between the roots of trees, beneath rocks, around old stumps, in holes in the ground and around houses and outbuildings. They have been found in the greatest numbers in the vicinity of human habitations. Occasionally they have been found in dark corners and in clothes closets in dwellings. In general they prefer dry, dimly lighted places.

WEB

The web is so distinctive that once it has been seen it may be recognized again at a glance. It is composed of very irregularly arranged, coarse threads which crisscross at various angles and in different planes. It is always found built in relation to a crevice or corner into which the spider, frequently by means of a poorly formed tunnel of silk, hurriedly retreats when disturbed. The web is relatively very strong and serves to entangle insects many times the size and weight of the spider. On many occasions I have observed large wood and water beetles and, in one case, a young mouse becoming entangled, swathed in silk and suspended in the web by these spiders. The web spun by the male is always smaller and weaker than that of the female.

FEEDING HABITS

When an insect becomes entangled in the web of the Latrodectus mactans, the spider, if not already fed to satiety, rushes out into the web to the immediate vicinity of the struggling victim. It then turns its back and, keeping at a safe distance, commences enswathing its prey in a mantle of silk. This is accomplished by the use of the long hind-legs which, in a rapid, alternate fashion, pull forth strands of silk from the spinnerets and cast them over the struggling insect. In the early stages of the struggle viscid silk[3] is used, which by its viscosity and

3. Viscid silk, a transparent semifluid material, is characteristic of the family Theridiidae. It is thrown over the victim by the comb on the hind tarsi and is supposed to be derived from the lobed silk glands which have been found only in this family (Comstock, J. H.: The Spider Book, New York, Doubleday, Page & Company, 1913, p. 333).

elasticity prevents any immediate escape. The victim's mo ents having then been further hampered by the addition of st. ls of finer silk, the spider approaches and seeks a point at which it n insert the claws of its chelicerae. This may be in the leg, the antenna or the body of the victim. The claws having been inserted and the ve om thereby injected, the spider retires to await the result. In the space of a few minutes the struggles cease. The spider leisurely returns, completes enswathing the victim in silk and hoists the body to the desired position in the web. Fastening its mouth parts to some portion of the body the spider then proceeds to suck the body fluids. A small insect, such as a fly, may be sucked dry in a little over an hour. A larger insect, such as a water beetle, may be fed on for a day or two. The dry, skeletal husk is then cut out and dropped from the web. The abdomen of the spider after feeding may be twice its original size.

These spiders are capable of going without food for over a month with no recognizable harmful effect. Their fluid requirements are supplied by the body fluids of their victims. They seem to prefer to feed at night, though when hungry they feed at any time. They do not attack or feed on insects immediately preceding, during or immediately following a moult. On its completion they are, however, voracious and feed until the abdomen swells up to double its previous size. While awaiting their prey they are usually found hanging in their web with the ventral surface uppermost. They are cannibalistic, feeding on each other whenever the opportunity presents itself. The common nickname "black widow" given to the female of this species arose from her habit of capturing and feeding on the much smaller male.

MATING

Though the actual process of impregnation has not been observed it apparently occurs in the fall or early in the spring. This conclusion is based on two facts. First, mature males are most plentiful in the fall, becoming progressively less so during the following winter, spring and summer. Second, many females captured in the fall and kept alone in captivity over the winter lay fertile eggs the following spring. This suggests that, in most cases, the male impregnates the female in the fall and then dies or is killed during the following winter and spring.

EGG SAC

The egg sac is a globular or pyriform case of silk (fig. 1 *A*) in which the eggs are loosely deposited. The laying of the eggs and the formation of the egg sac invariably took place at night. As a consequence the first steps in the formation of the egg sac have not been observed. In the early stages, however, it consists of a delicate, transparent mesh

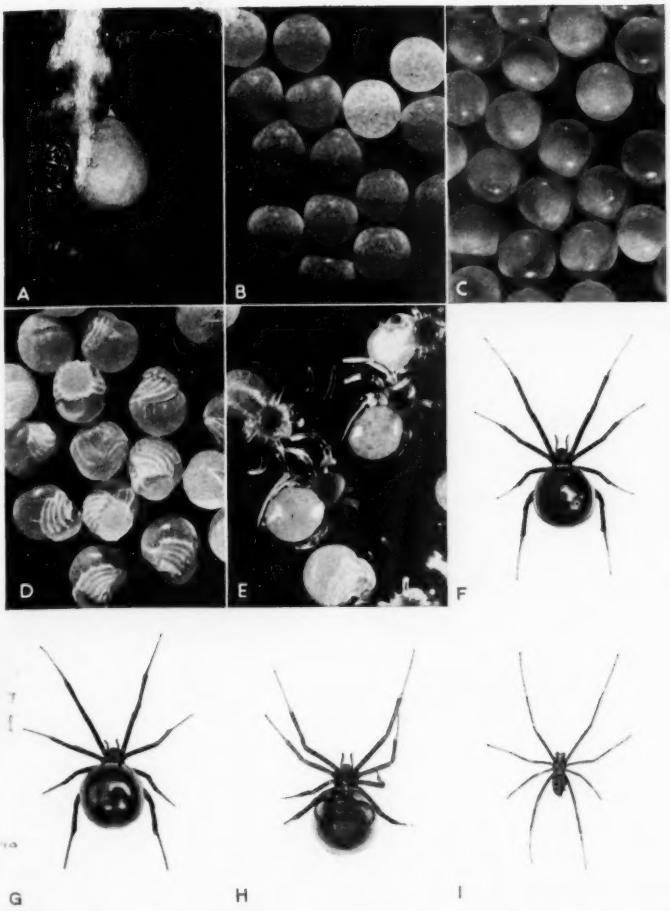

Fig. 1.—*A*, egg sac; reduced from × 1. *B*, eggs, first day after laying, showing speckled appearance; reduced from × 10. *C*, eggs, seventh day after laying, showing white discoid formation; reduced from × 10. *D*, eggs, tenth day after laying, showing formation of cephalothorax. In some eggs the enveloping membrane has split, and the legs are beginning to emerge; reduced from × 10. *E*, spiderlings emerged from egg membrane, eleven days after laying; reduced from × 10. *F*, dorsal view of a large female which, although almost full grown, still has the red markings up the midline; reduced from × 1. *G*, dorsal view of adult female showing the characteristic glossy, solid black appearance; reduced from × 1. *H*, ventral view of adult female showing the characteristic red markings on the under surface of the abdomen; reduced from × 1. *I*, dorsal view of adult male. Note the size relative to that of the adult female, the clear bands on the legs, the anteriorly placed genital bulbs and the characteristic abdominal markings; reduced from × 1.

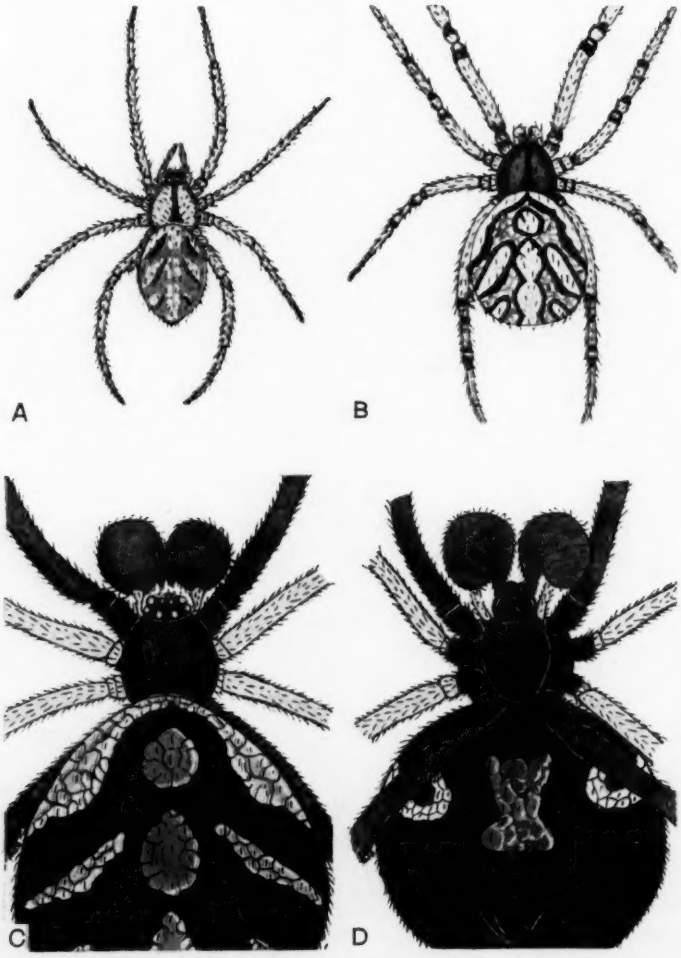

Fig. 2.—Series of spiderlings to demonstrate color development. *A*, spiderling just prior to the second molt about the time of emergence from the egg sac; reduced from × 20. *B*, spiderling twenty-one days later, just prior to the third molt. At this time no distinction between male and female could be discerned; reduced from × 20. *C*, dorsal view of spiderling immediately after the fourth molt. The tibias of the palpi are now swollen to form the genital bulbs indicative of a male. The color markings of both male and female spiderlings at this period are, however, the same. These markings remain in the male but are lost in the female; reduced from × 20. *D*, ventral view of spiderling as seen in *C*, showing color marking common to both male and female; reduced from × 20.

of silk through which the enclosed mass of eggs may be seen. The wall of the sac is then thickened and rendered opaque by a closely knit weave of fine viscid silk. The deposition of this viscid silk is accomplished by a rapid tapping action of the abdomen which brings the spinnerets situated at its tip into contact with the surface of the egg sac. The viscid silk hardens on drying, fixing the contour of the sac and producing an outer semirigid wall. The whole process from the laying of the eggs to the completion of the egg sac occupies less than twenty-four hours. The color of the egg sac is usually a creamy white when first formed, but darkens to a light tan with age. It hangs firmly suspended in the web by silken cords. The mother is usually found close by, with one or more legs placed protectingly on its surface.

The female Latrodectus mactans does not die after laying a mass of eggs and forming an egg sac. If well fed she may form a second egg sac filled with fertile eggs within nine days of the first. One female formed three egg sacs while under observation in captivity. Since one egg sac may contain over six hundred fertile eggs, the number of spiderlings which may arise from one female may number thousands. There is wide variation in the size of the egg sacs and the number of eggs contained.

EGGS

The eggs are round, translucent and approximately 1 mm. in diameter (fig. 1 *B*). The color of the eggs varies from a creamy white to a pale mauve. The cause of this variation was not determined and has no apparent significance for the course of future development. The eggs have a hard covering protecting the semifluid content and when dropped on a hard surface bounce and roll with no apparent injury. The number of eggs laid at any one time varies from less than one hundred to more than six hundred. The chief egg-laying season is spring and early summer, though so long as the weather remains warm, fresh egg sacs continue to be formed by newly matured females.

The eggs of Latrodectus mactans are very poisonous. Two eggs crushed and emulsified in a drop of saline solution were found sufficient to kill an adult white mouse when injected intraperitoneally. A few drops of a saline emulsion of eggs injected intravenously kills a rabbit in two minutes.

DEVELOPMENT

The eggs when first laid are speckled with flecks of a white flocculent material (fig. 1 *B*) lying in the semifluid egg contents immediately beneath the transparent egg covering. During the next few days this material coalesces to form a white, discoid mass near the upper surface of the egg (fig.1 *C*). Approximately ten days after the eggs have been laid this mass suddenly enlarges and projects as a knob from the globular

surface of the egg. The membranous covering of the egg becomes wrinkled in this region, and beneath it the outlines of the cephalothorax and appendages become clearly discernible. By the following day the enlarging cephalothorax has split the membranous egg covering (fig. 1 *D*). The split enlarges, and in twenty-four hours the spiderling emerges (fig. 1 *E*). During the hot summer weather ten or eleven days is the average period for hatching. Cold weather, however, lengthens the period, and if the cold is sufficiently severe or prolonged, hatching may never occur.

Subsequent development of the newly hatched spiderlings is marked by a series of moults accompanied by a gradual increase in size and in pigmentation. The early modification of the palpi to form secondary sex organs serves to differentiate the male from the female.

After hatching the spiderlings remain in the egg sac. There they undergo their first moult approximately five days later. Prior to this movements are feeble, hairs are absent, and pigmentation is scanty. Following the first moult the spiderlings become increasingly active and finally, after making a pinhole opening in the egg sac, emerge one by one, spinning a fine web as they go. In warm weather this process takes place about twenty-five days after the eggs are laid. The second moult takes place outside the egg sac a few days after the spiderlings have emerged. When they first emerge from the egg sac they cluster in their finespun web, but after the second moult they commence to separate and seek a home for themselves.

Prior to the second moult nourishment for their growth is provided by that already present in the globose abdomen. After the second moult, however, this source is depleted as evidenced by the shrunken abdomen, and they commence to attack and to feed on one another unless more accessible food is available. The mother of the brood makes no attempt to provide them with food and may herself feed on them. The mortality rate is thus very high.

Six moults are usually required for complete development. The interval between moults varies with the amount of food available. In the early stages of development the food supply being nearly equal for all, the interval is correspondingly more uniform. Later, however, the wide variations in the food supply of each spider produce a corresponding irregularity in the moulting intervals. In the early stages the interval is usually from fifteen to twenty days, but later it may be a month or more.

The cephalothorax and appendages of the newly hatched spiderling are crystal white (fig. 1 *E*). The globose abdomen may be creamy white or reddish grown. It is flecked with white flocculent masses which early become collected on the ventral surface, down the midline of the dorsal surface and in stripes on the side of the abdomen. As

growth proceeds an orange and later a red color appears in these regions. The rest of the body in the meanwhile becomes gradually suffused with a black pigment. This pigment first appears on the region of the ocular tubercle, the region around the spinnerets, the tips of the chelicerae and mouth parts, down the midline of the dorsal surface of the cephalothorax and on the tips and joints of the appendages (fig. 2 *A* and *B*). Prior to the fourth moult no indication of the sex of the spiderling is furnished by the color markings or external structures. The color markings of the spiderlings are retained in large measure by the adult male. Thus the male has, in addition to the red, ventral, abdominal marking, common to both sexes, a row of orange red spots down the midline of the dorsal surface of the abdomen, three orange-yellow side stripes on the abdomen and clear straw-colored bands on its legs (fig. 1 *I* and fig. 2 *C* and *D*). All these color markings are likewise possessed by the immature female. Later, however, they are lost in a general suffusion of black pigment, only the ventral red marking and that over the spinneret remaining in the adult female (fig. 1 *G* and *H*).

At the fourth moult the tibia of the palpi of a male spiderling suddenly expands to form a yellowish or olive green bulbous structure (fig. 2 *C* and *D*). This swelling involves to a lesser extent the tarsus and the patella. The tarsus appears as the pointed extremity and the patella as the expanded cap of the bulb. After the fourth moult, though the color markings of male and female may be similar, the modification of the male palpi to form secondary sex organs serves as an infallible guide to the sex of the spider. At the fifth moult the secondary sex organs of the male undergo a second remarkable transformation. In place of a rounded bulbous structure a complex structure with a spiraled cuplike opening appears. It is used for the storage and later the transference of seminal fluid to the spermathecae of the female at the time of mating. With its appearance the male may be regarded as an adult, though further increase of size occurs. The development of these adult sex organs is attained in from two to three months. The maturation of the male is somewhat more rapid than that of the female.

SPAN OF LIFE

The life span of the female is approximately one year. If hatched early in the spring the spiderling may, if the food supply is adequate, mature by late summer, live over the winter, lay its eggs the following spring and die during the summer or fall.

The life span of the male is usually less than a year. If hatched early in the spring it matures during the summer, mates and dies during the fall or winter.

DANGER TO MAN

In man the bite of Latrodectus mactans is followed, with dramatic suddenness, by a characteristic and alarmingly severe systemic reaction.[4] The full grown female, particularly when distended with eggs, appears from experiments with animals, to be the most poisonous. It is, however, a timid creature and when disturbed makes every attempt to escape. This explains the relatively small number of bites in spite of the prevalence of these spiders in this section. When cornered or compressed, as between the skin and clothing, the spider bites in self-defense. Bites about the genitals are frequent on persons using an outdoor privy across the seat of which one of these spiders has spun its web. The frequency with which "the black widow" is found around and in human habitations constitutes a potential danger. The male, though also poisonous, may, on account of its size, greater timidity and scarcity, be ignored as an etiologic factor of any importance in arachnidism.

SUMMARY

Latrodectus mactans is the only proved poisonous spider found in the United States. No complete study of its life history has, however, so far been made. For the past two years a study of this spider as found in the vicinity of Tuscaloosa, Ala., has been made. Observations, accompanied by illustrations, on its appearance, habitat, web, feeding habits, mating, egg sac, eggs, development, span of life and danger to man are presented.

University of Alabama.

4. Baerg.[1] Blair.[1] Bogen.[2]

PERNICIOUS ANEMIA

RESULTS OF TREATMENT OF THE NEUROLOGIC COMPLICATIONS

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AND
ERNESTINE KANDEL, M.D.*
CHICAGO

The introduction of liver for the treatment of pernicious anemia by Minot and Murphy has provided an efficacious method of increasing the number of red blood cells and the percentage of hemoglobin to figures approaching normal, thereby relieving the general asthenic symptoms and prolonging the lives of patients indefinitely. The effect of liver on the neurologic complications of pernicious anemia also has been studied with great interest, but with the use of less certain criteria on which conclusions may be based. The literature already contains reports of several studies carried out over long periods of time which seem to indicate both prophylactic and curative values of liver extracts on the neurologic complications. However, some clinicians attributed an indirect action to the liver and suggested that the usual gain in general strength enhances the patient's powers of compensation for his neurologic defects, while others denied any noteworthy change in the nervous symptomatology. Perusal of the published data reveals an almost complete absence of adequate neurologic studies of patients over a long period of time. In many instances only one careful neurologic examination was performed, or observations before and after therapy were not made by the same examiner.

In 1927, Koessler and Maurer [1] used a diet which was rich in vitamins A, B and C for the treatment of pernicious anemia, but which was virtually liver treatment because from 100 to 250 Gm. of liver was prescribed daily to insure an adequate supply of vitamin A. From the practice of one of us (R. R. G.) 2 patients were reported in whom striking improvement occurred, so that they were able to walk after a fashion although they had previously been bedridden. Improvement

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* Douglas Smith Fellow.

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1. Koessler, K. K., and Maurer, S.: The Treatment of Pernicious Anemia with High Caloric Diet Rich in Vitamins, J. A. M. A. **89**:768 (Sept. 3) 1927.

in strength and ability to get around was not accompanied by noteworthy change in the objective neurologic status.

Bubert [2] reported a case frequently quoted as showing neurologic regeneration induced by the use of liver. The description of the course of the nervous symptoms and signs included not only contradictions but also evaluations of the effects of therapy by neurologists who had not examined the patient before. The objective evidence of improvement consisted largely in the return of knee jerks, while at the same time the abdominal and cremasteric reflexes were lost, obviously suggesting not improvement but progression of the lesion to the lateral tracts. The case of Mason [3] is another example of poorly controlled observations on the changing neurologic status, and yet it was used as evidence of possible improvement of cord symptoms by treatment.

Richardson [4] recorded 67 cases of pernicious anemia, 14 of which showed ataxia. Seven of these he considered as showing severe cord changes. "The patient's statement as to his ability to get around and do his work was taken as evidence of improvement, even though the objective signs might still be present." On this basis 8 patients with ataxia were moderately improved and 2 showed no change. Starr [5] reported 8 cases of combined degeneration of the spinal cord which had been studied for three years. On adequate liver therapy, with the blood count maintained at a high level, the condition in 4 cases remained stationary and showed no increase in neurologic signs. A like number in which the blood count was always low showed progressive neurologic changes. The conclusion was drawn that adequate liver therapy may have a preventive effect on degeneration of the cord.

Minot and Murphy,[6] in a discussion concerning 105 treated patients, stated that it was their experience that neural symptoms developed in few patients receiving therapy and that no extension or aggravation of a preexisting lesion occurred after one month of therapy. They quoted 2 exceptions, cases in which the involvement of the spinal cord was extreme but ascribed to neglect of diet. "Of course, changes in reflexes have remained present," they stated. Coordination of the extremities had distinctly improved in many cases, but Minot and Murphy stated that although neurologic improvement has occurred with liver therapy, the ability to walk after having been bedridden was prob-

2. Bubert, H. M.: Subacute Combined Sclerosis, J. A. M. A. **90**:903 (March 24) 1928.

3. Mason, E. H.: Pernicious Anemia, J. A. M. A. **90**:1527 (May 12) 1928.

4. Richardson, E.: Pernicious Anemia, New England J. Med. **200**:540, 1929.

5. Starr, P.: The Prevention of Spinal Cord Degeneration in Pernicious Anemia, J. A. M. A. **96**:1219 (April 11) 1931.

6. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927.

ably due to improvement of muscular strength from a continuously high level of red blood cells. In summary they stated, "Improvement in neural symptoms has been most gratifying to the patient," and such symptoms had not definitely progressed or developed under adequate dietary treatment (200 Gm. or more a day).

Smithburn and Zerfas [7] reported a study of 115 cases of pernicious anemia. The mental condition improved rapidly on liver therapy, although a few patients persisted in having ideas of persecution over a period of several months. These workers observed that no tendon reflexes changed while the patient was under treatment, except that in several instances diminished reflexes disappeared entirely; but when hyperactive, the reflexes remained so or became progressively worse. Improvement was seen most frequently in paresthesia. Improvement in ataxia, sphincteric control and psychic changes was considered the result of betterment of the muscular strength and general condition, due to the normal blood range, especially since in 13 cases ataxia was unaccompanied by any other defect and was attributable to weakness rather than to a central lesion. Davidson, McCrie and Gullard [8] expressed the opinion that symptoms referable to the nervous system, if of recent date and in the nature of mild paresthesia, may completely disappear. However, when they are the result of actual destruction of the nerve tissue no cure can be expected.

Sturgis, Isaacs and Smith [9] stated that in a series of patients with pernicious anemia with signs and symptoms of combined or lateral degeneration of the cord the administration of liver or liver extract produced no change in neurologic signs, although regeneration of the blood followed the usual course. However, early signs of involvement of the cord were followed by improvement after treatment with liver and physical therapy. The latter procedure was designed to strengthen the muscles and develop their control. Sturgis and Isaacs [10] stated elsewhere that patients with paresthesia are often helped by liver and ventriculin therapy. "In general it may be concluded that improvement in the minor neurological symptoms frequently occurs, but in patients with more extensive involvement, the outlook is far less promising."

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7. Smithburn, K. C., and Zerfas, L. A.: Neural Symptoms and Signs in Pernicious Anemia, Arch. Neurol. & Psychiat. **25**:1100 (May) 1931.

8. Davidson, G.; McCrie, J. G., and Gullard, G. L.: The Treatment of Pernicious Anemia: Liver Diet, Lancet **1**:847, 1928.

9. Sturgis, C. C.; Isaacs, R., and Smith, M.: The Treatment of Pernicious Anemia with Liver Extract, Ann. Int. Med. **1**:994, 1927.

10. Sturgis, C. C., and Isaacs, R.: Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract, Ann. Int. Med. **5**:131, 1931.

In 1930, Baker, Bordley and Longcope [11] reviewed the histories of 44 cases of pernicious anemia of which 39 showed evidence of involvement of the nervous system. The patients were studied during varying periods of liver therapy ranging from six to forty months. Improvement was reported in 61.5 per cent and no improvement in 36 per cent. The percentage of improvement was much higher in a group of patients treated longer than six months. Evidence of improvement cited included diminution of paresthesia, a change from ataxic to normal gait, a decrease in sphincteric disturbances, the disappearance of spasticity, the recovery of cutaneous sensibility and a change in the Babinski response from positive to "improved." Reduction in the quantity of liver ingested resulted in the relapse of the organic neurologic signs.

Ungley and Suzman [12] reported 61 cases of pernicious anemia with degeneration of the cord; 30 of the patients were treated with liver and compared with 31 who were observed for two years prior to the "liver period." Of the untreated patients none improved, 3 showed progression and 28 died. Of those treated with liver, 17 improved, in 8 the condition remained stationary or became worse, and 5 died. Numbness and tingling disappeared in practically all cases. The Babinski responses were lost in 5 cases, cutaneous sensation became normal in 8 and sphincteric disturbances disappeared in 6. The authors called attention to the phenomenal response of the nervous system to therapy on the twelfth day of the initial liver treatment. This is, of course, the time when the increase in red cells manifests itself in increased general strength and power of the patient. Nevertheless, the authors stated their belief that liver has a specific effect on the lesions of the cord caused by pernicious anemia.

Farquharson and Graham [13] reported 18 cases exhibiting well defined signs of subacute combined degeneration. They concluded that "adequate liver therapy has a specific effect on the nervous system lesions, arresting their progress in virtually all cases and causing marked improvement in large numbers." However, complete recovery had not occurred after definite nervous manifestations, "but liver extract not only cures the anemia but prevents the subsequent development of subacute combined degeneration of the cord. It arrests the progress of existing nerve lesions and in many instances results in marked improvement of the nervous signs and symptoms, more particularly those of

11. Baker, B. M.; Bordley, J., and Longcope, W. T.: The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, Am. J. M. Sc. **184**:1, 1932.

12. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effect of Liver Therapy, Brain **52**:271, 1929.

13. Farquharson, M. B., and Graham, D.: Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, Canad. M. A. J. **25**:237, 1930.

relatively short duration." Under the improved organic signs the authors included paresthesia, objective sensory changes in reflexes, ataxia and signs of disease of the pyramidal tract. Progress of the neurologic defect was attributed to an insufficient quantity of liver (an adequate dosage was considered to be the juice from 1 pound [453 Gm.] of liver a day). The greatest improvement in neurologic signs and symptoms occurred after the second month of therapy. The authors did not agree that general improvement of strength could account for the striking improvement in the neurologic states of their patients.

The obviously conflicting reports concerning the effect of the feeding of liver on the neurologic complications of pernicious anemia stimulated us to organize a special clinic for the study of such cases at the University of Chicago. In the two and a half years of operation there have been studied in our clinic over 50 cases of combined degeneration of the cord and numerous cases of pernicious anemia uncomplicated by neurologic lesions.

Most of the patients were first hospitalized for a month and given liver extract or ventriculin in order to raise the blood count rapidly. After discharge from the hospital, varying amounts of liver extract or the domestic extract of liver were given. The term "adequate therapy" used throughout the paper is understood to mean a sufficient quantity of liver to maintain a normal blood level together with that feeling of well-being peculiar to health. This has at times meant a change in the amount of liver given, as indicated in the table as the average dosage for the period. Many patients during epidemics of colds required additional liver, while several whose blood value had been slightly over the normal level complained of heaviness with an annoying hot sensation, requested a reduction in the intake of liver.

We have in most cases not otherwise indicated given the lowest level of the red cell count for the period after the blood once reached normal limits. The patients for the most part were able to maintain a red cell count within a few hundred thousand on either side of the accepted normal limits.

Careful neurologic reexaminations were made at regular intervals, often twice a month or, as time went on, once a month. The cases reported here were selected from those of undoubted pernicious anemia showing variable degrees of anemia, an atrophic tongue, achlorhydria, as demonstrated by the histamine test, and a typical blood smear.

UNCHANGED CASES

In the table are outlined the essential neurologic data concerning 19 cases of pernicious anemia with complications referable to the nervous system. The ages ranged from 37 to 73 years. Among the findings were signs and symptoms referable to the posterior and lateral columns

Data on Nineteen Cases of Combined Degeneration of the Cord Treated with Liver Without Change in Neurologic Status

Case	Age and Sex	Previous Duration	Weakness	Dysesthesias	Red Blood Cells; Hemoglobin	Muscle Tone	Deep Reflexes in the Legs	Babinski Reflex	Clonus	Position Sense	Vibration Sense	Cutaneous Sense	Ataxia	Romberg Sign	Liver Therapy
1	60 M	2 months Sudden onset	+	+ (hands) 2 days	1,580,000 50%	—	Decreased	—	—	Poor in feet	Dim below 12th dorsal	Hyperalgesia in legs	+++	+	1 lb. daily from Nov. 2, 1931, to Jan. 10, 1933; red cell count, 4,100,000; hemoglobin, 93%
2	55 F	2 years Irregular liver therapy for 14 mos.	+ 2 yrs.	+ 1 yr.	2,980,000 70%	—	+++	+ Bilateral	+	Poor in legs	Absent below patella	—	—	+	Domestic extract, 1 lb. daily for 6 mos.; red cell count, 4,800,000; hemoglobin, 101%
3	45 M	1 year	+	+ 1 yr.	5,010,000 90%	Increased	++++	—	—	—	Diminished	Decreased in legs	++	+	1 lb. daily for 15 mos.; maintained count
4	37 F	4 years	—	++ 18 mos.	4,500,000 87% (for 2 yrs.)	Spastic legs	++++	+ Bilateral	+ Bilateral	Decreased ++	Decreased ++	Hyperalgesia in hands	+	+	1 lb. daily for a total of 3 yrs.
5	45 M	6 months Treated as tabes dorsalis	+	+	4,400,000 87%	—	Achilles 0; knee jerks, unequal	+ Bilateral	—	Decreased	Decreased	—	+	+	Daily for 22 mos.; reflexes became exaggerated; red cell count, 4,700,000; hemoglobin, 94%
6	59 F	7 years Diagnosed as pernicious anemia	+	+	4,500,000 90%	—	Achilles 0; knee jerks decreased	—	—	Decreased	Absent below knees	—	+	+	1 lb. daily for 2 yrs.; maintained count
7	60 F	5 years Irregular liver therapy	++	—	3,300,000 67%	—	Decreased	? Left	—	Decreased	—	—	—	+	1 yr. and 8 mos.; red cell count, 4,300,000; hemoglobin, 80%
8	63 M	6 weeks	—	++	3,480,000 63%	—	Decreased left achilles 0	+ Bilateral	—	Decreased in legs	Decreased in legs	Decreased in hands	—	+	15 mos.; red cell count, 4,400,000; hemoglobin, 83%
9	59 M	2 years	+	++	4,400,000 85%	—	—	—	—	—	Deficient	—	—	—	27 mos.; 3 vials of oral extract daily
10	64 M	6 months	—	++	4,600,000 62%	Spastic	+++	—	—	—	Absent in legs	—	++	++	32 mos.; 3 vials of Lilly's oral extract daily; red cell count, 4,900,000; hemoglobin, 100%
11	64 M	2 years	++	++	2,200,000 53%	Slightly spastic	Decreased	+	—	Decreased	Decreased	—	Slight	+	20 mos.; red cell count, 4,100,000; hemoglobin, 75%
12	73 M	2 months	++	++	3,900,000 60%	—	—	—	—	Decreased	Decreased	Hyperalgesia in fingers	—	+	26 mos.; red cell count, 4,400,000; hemoglobin, 90%
13	64 M	4 months	+	++	3,100,000 85%	—	—	—	—	—	Decreased	Hyperalgesia in fingers	—	—	6 mos.; red cell count, 4,700,000; hemoglobin, 92%
14	58 F	18 months	+	+	2,090,000 51%	Spastic	+++	—	—	Poor	Absent below 7th dorsal	—	+	+	6 mos.; red cell count, 4,100,000; hemoglobin, 80%
15	49 M	4 years	+	+	3,400,000 84%	Spastic	++++	+	+	Absent in legs	Lost below 12th dorsal	Decreased in fingers and legs	+	+	19 mos.; red cell count, 4,700,000; hemoglobin, 92%
16	44 F	4 years	+	+	4,900,000 91%	—	+++	—	—	Decreased	Decreased	—	—	—	6 mos.; red cell count, 4,980,000; hemoglobin, 97%
17	66 F	2 years	+	+	1,700,000 34%	Increased	++++	—	—	Absent in feet	Absent below knees	—	—	+	6 mos.; red cell count, 4,300,000; hemoglobin, 73%
18	49 M	2 years	+	+	4,900,000 78%	—	+	—	—	Decreased	Decreased	—	—	+	2 yrs. and 6 mos.
19	54 M	6 weeks	+	+	3,200,000 60%	—	+++	+ Bilateral	—	Reduced in feet	Reduced below knees	—	—	—	2 yrs.; red cell count, 4,800,000; hemoglobin, 99%

and varying combinations of these. The patients were treated with a pound of liver or a domestic extract of liver daily for from six months to three years. In all, the blood count and hemoglobin percentage were maintained at a high level. However, in none of these cases was there the slightest change in any sign of organic disease, including the great variety of signs which have been reported as improved under therapy by other observers.

In those in whom the blood count was low at our first observation therapy resulted in a concomitant increase in general strength, but not the slightest effect on the neurologic signs was noted.

CASES PROGRESSING UNDER THERAPY

The following cases are examples of progression in neurologic signs and symptoms in spite of vigorous and controlled liver therapy consisting of a pound of fresh liver or its equivalent daily over periods ranging from six months to two years. The case histories, briefly cited, indicate the nature of the signs and symptoms unaffected by the therapy and the new disabilities appearing during treatment.

CASE 20.—A man, aged 67, was first seen on May 18, 1931, complaining of easy fatigue of one year's duration. He had some dizziness and dyspnea on exertion, but no neurologic complaints. Examination showed a red cell count of 2,600,000, 53 per cent hemoglobin and many macrocytes, hyperchromasia and a polymorphonuclear shift to the right in the smear. There was no free gastric acidity. Neurologic examination gave a negative result.

Course.—The domestic liver extract first used by Castle and Bowie [14] (prepared from 1 pound of beef liver) was administered daily. The blood count rose to 4,100,000 red cells per cubic centimeter, and the hemoglobin to 75 per cent and finally to 92 per cent. However, on Sept. 26, 1932, the patient had marked numbness and tingling in the legs and marked disturbances in coordinate movements of the legs. The patellar jerks were exaggerated, the Romberg sign was positive, and sense of vibration was absent below the knees. Evidences of combined degeneration of the cord had developed while the patient was receiving adequate treatment with liver.

CASE 21.—A man, 54 years of age, was first seen in June 1930 with the complaints of weakness, shortness of breath and numbness in the extremities of six months' duration. Examination showed a lemon-yellow color of the body, an atrophic tongue and achlorhydria. The blood count showed 1,050,000 red cells, 37 per cent hemoglobin, and anisocytosis, poikilocytosis, hyperchromasia and macrocytes in the smear. Neurologic examination showed active deep reflexes, a positive Romberg sign and loss of vibratory sense below the twelfth dorsal segment.

Course.—In twenty-six days ventriculin brought the red cell count to 3,600,000 and the hemoglobin to 79 per cent. Later, both the red cell count and the hemoglobin were within normal limits. The equivalent of a pound of liver a day was used for two years and three months, but in spite of this, on Oct. 14, 1932, there were found great spasticity in both legs, a bilateral Babinski sign and absent knee

14. Castle, W. B., and Bowie, M. A.: A Domestic Liver Extract for Use in Pernicious Anemia, J. A. M. A. **92**:1830 (June 1) 1929.

and ankle jerks, although the blood count and percentage of hemoglobin had remained normal. Serious progression had occurred under therapy.

CASE 22.—A woman, aged 47, entered the clinic in January 1931 after having symptoms of fatigue for three years, heaviness in the legs, numbness, tingling and uncertainty of the position of the extremities. The red cell count was 4,080,000, the hemoglobin was 85 per cent, and in the blood smear macrocytes and a shift to the right were seen. There was no free gastric acidity. The patient had spastic paraplegia with exaggerated deep reflexes, positive Babinski and Romberg signs, a decreased sense of position in the legs and absent vibration sense below the twelfth dorsal segment.

Course.—For two years the patient faithfully took domestic extract from 1 pound of liver a day and showed no improvement, but a slowly progressive increase in sensory symptoms. The sense of position became more grossly disturbed in both legs.

CASE 23.—A woman, 51 years of age, entered the clinic on Oct. 17, 1930, stating that for six months she had noticed an increasing weakness and change in color. Examination showed a lemon-yellow color, an atrophic tongue, achlorhydria, a hemoglobin value of 87 per cent, and a red cell count of 4,360,000. There were macrocytes and a shift to the right in the blood smear. Neurologic examination showed exaggerated patellar and achilles jerks, a positive Babinski sign on the left and definite spasticity of the legs. Vibration was not felt below the twelfth dorsal segment and the sense of position was disturbed in the legs, so that the gait was that of spasticity plus ataxia.

Course.—At first, six vials of liver extract and rest in bed for three weeks were prescribed, and then domestic extract of 1 pound of liver a day was taken continuously, with the exception of two months, for fifteen months. Yet on April 3, 1931, the patient's ataxia was increased, the feet were uncontrollable and she struck one ankle with the other on walking. Sewing was impossible. A constricting sensation appeared about the knees, and numbness increased. The exaggeration of deep reflexes was increased, and patellar and ankle clonus were elicited. Vibration was then absent below the seventh dorsal segment. On October 5, the Babinski sign was bilaterally positive and the symptoms referable to the lateral and posterior columns were worse.

CASE 24.—A woman, 48 years of age, entered the clinic on Feb. 11, 1931, complaining of weakness of one year's duration (during which time Lilly's liver extract had been taken) and tingling and numbness in the feet and hands for three months, with some difficulty in walking. On entrance the red cell count was 3,200,000 and the hemoglobin 63 per cent. In the blood smear a shift to the right and macrocytosis were found. There was no free acid in the gastric contents, and the spleen was barely palpable. The deep reflexes were reduced and the ankle jerks absent. A positive Romberg sign was elicited, and vibratory sensation was absent below the fourth lumbar segment. The skin of the lower extremities was hyperesthetic.

Course.—For three weeks from six to nine vials of Lilly's liver extract were taken daily, bringing the blood count to 5,000,000 and the hemoglobin to 90 per cent. Then a pound of liver was given each day in the form of domestic extract, so that at the time of this report the patient had been receiving adequate liver treatment for twenty-three months. In spite of this treament, on Dec. 2, 1931, vibratory sense was decreased, the disability extending to the twelfth dorsal segment. Sense of position and coordination became affected, so that she could walk only with difficulty. On Oct. 24, 1932, the patellar reflexes were exaggerated, but the ankle jerks were still absent. Progression had occurred in the sensory sphere, and signs referable to the lateral tract had appeared.

CASE 25.—A man, aged 60, had noted anorexia, dizziness and weakness for two months, associated with the sudden onset of burning of the tongue and a yellow skin. Examination on Nov. 2, 1931, revealed no free gastric acidity, a red cell count of 1,580,000 and a hemoglobin content of 56 per cent. The deep reflexes were reduced, sense of vibration was diminished below the iliac crests, and the skin of the legs was hyperalgesic. Sense of position was impaired in the toes, and the Romberg sign was slightly positive. With the use of Lilly's liver extract, nine vials a day, the red cell count was brought up to 4,000,000 and the hemoglobin value to 85 per cent in fifteen days, and they remained at this level. One pound of domestic extract of liver was used each day for fourteen months. In spite of this, on June 10, 1932, the patient had greater difficulty in walking, the Romberg sign was grossly positive, and the vibratory defect had ascended to the level of the seventh dorsal segment.

CASE 26.—A man, aged 43, entered the clinic on Aug. 28, 1931, complaining of dyspnea, weakness, ease of fatigue, heavy sensations and numbness of the hands and feet, a sore tongue and impaired appetite for about six months. Examination showed an atrophic tongue, an enlarged spleen and pitting edema of the ankles. The red cell count was 2,200,000, and a smear showed anisocytosis, poikilocytosis, macrocytes and a shift to the right; the hemoglobin was 45 per cent. No free gastric hydrochloric acid was shown by the histamine test. The deep reflexes were all reduced; the Babinski response was negative. Sensation was normal except for reduced vibration sensibility in the lower part of the legs, and coordination was good.

Course.—A good response was obtained with Lilly's liver extract, so that the red cell count was brought up to 4,400,000 and the hemoglobin to 84 per cent in two months, where they remained for the period of observation (fifteen months). Either domestic extract of 1 pound of liver or three vials of Lilly's liver extract were used daily. In spite of this, on April 8, 1932, the Babinski response was found to be bilaterally positive. Since then no change in the condition has appeared.

CASE 27.—A woman, aged 44, was first seen in May 1930, at which time she gave a history of loss of appetite, weakness, tingling in the hands and feet, shortness of breath and a yellow color of fifteen months' duration. During this period liver therapy had been carried on under her physician's direction. Three weeks prior to admission the symptoms increased.

Examination revealed a pale yellowish skin, an atrophic tongue, an enlarged spleen and a rapid heart rate. The deep reflexes were equal and lively; the superficial reflexes, present. Sense of position and other sensory modalities were normal, and coordination was good. The Babinski responses were negative. Mental symptoms in the form of irritability and a decrease in memory were noted. The gastric contents contained no free hydrochloric acid, even with histamine. The red cell count was 1,500,000 and the hemoglobin 30 per cent; the leukocytes numbered 6,000 per cubic millimeter. Blood smears showed marked difference in the size and coloring of the red cells and a shift to the right.

Course.—Four vials of ventriculin were given each day, with a reticulocyte response of 48.4 per cent on the seventh day. After three weeks the red cell count was 3,600,000 and the hemoglobin 70 per cent, later rising considerably more. The mental symptoms and paresthesia entirely disappeared, but the neurologic signs were unchanged. The dosage of ventriculin, four vials a day, was continued, but in February 1931, ten months later, reexamination showed an increase in neurologic signs. A bilaterally positive Babinski sign had appeared, and vibratory sense was reduced in the lower extremities. In spite of this the blood count, hemoglobin

and general strength remained normal. In December 1931, the patient returned, after neglecting her treatment for three months, with a relapse in the blood picture but no increase in neurologic signs. For the next twelve months she used the domestic extract of a pound of liver each day, with no change in her condition except the disappearance of paresthesia and a general feeling of renewed strength.

Case 28.—A man, 49 years of age, was admitted to Billings Hospital in September 1931, unable to walk. About six months previously he had begun to have a sense of dizziness, and finally had to give up work because of a feeling of insecurity. He was told that he had anemia, but was not treated until six weeks later when he went to a hospital, at which time he was given three vials of Lilly's liver extract a day. He improved and left the hospital after four weeks. After using liver extract, three vials a day for six weeks, the amount was reduced to two vials and then only one a day was taken. Six weeks previous to admission to Billings Hospital he began to have sensations of numbness and tingling over the hands and feet and lower part of the abdomen. This disappeared in a few weeks, and he began to notice a change in his gait, for it became increasingly difficult to walk.

During examination the patient was easily confused; he was unable to think of words, and his memory was poor. The tongue was bright red at the margins and atrophic. The liver and spleen were not palpable. There was redness of the left buttock with oozing from a few areas the size of a pinhead. There was moderate muscular weakness throughout. Spasticity was great and could not be overcome by force; there were ankle and patellar clonus. The Babinski sign was present bilaterally; the abdominal and cremasteric reflexes were absent. Very slight defense reflexes were present. There was a patchy preservation of the sense of pain in the legs; otherwise it was almost totally absent. Hypesthesia and hypalgesia were noted from the first lumbar to the fifth dorsal level, and there was hypesthesia of the hands and lower part of the forearms. Vibratory sense was absent below the eleventh dorsal vertebra. There were incoordination and loss of sense of position in the upper and lower extremities. The flow of urine was difficult to start.

The hemoglobin was 75 per cent; the red cell count 3,700,000, and the white cell count, 5,850. Smears showed anisocytosis and poikilocytosis with a few macrocytes; regeneration of the blood seemed active. There were polychromasia and an occasional nucleated red cell. The urine showed albumin with both white and red blood cells. The Wassermann and Kahn tests gave negative results in both the blood and the spinal fluid. The Ewald and histamine tests showed no free hydrochloric acid.

Course.—After the obvious diagnosis of pernicious anemia with combined degeneration of the cord was made, a liver extract which was not a potent substance was given for nine days. There was an increase in the areas of redness over the buttocks, hips and heels. Symptoms increased in the bladder and edema was beginning on the lower extremities. Lilly's liver extract was administered first on Sept. 24, 1931. Six vials were given each day. In five days the reticulocyte peak was revealed at 11 per cent. Smears showed more macrocytes, and there was a more definite shift to the right. A septic temperature developed, and on September 29 an inlying catheter was inserted. The hemoglobin was 60 per cent, the red cell count, 3,100,000, and the white cell count, 9,800. From this time on there was a progressive increase in all symptoms, probably owing to the infection. Edema of the legs was marked, and there was a reduction of plasma protein to 5.96 Gm. per hundred cubic centimeters on October 19, 5.71 Gm. on December 2

and 6.69 Gm. on December 11. There was a steady decrease in hemoglobin and in the red cell count on liver therapy. Decubitus ulcers sloughed increasingly, for which symptomatic treatment was given. The sensory loss extended upward to the second dorsal level. On December 12, the hemoglobin was 35 per cent; the red cell count, 2,000,000, and the white cell count, 21,000. Hypostatic pneumonia eventually developed, and the patient died on December 18, with no further change in objective neurologic findings.

Autopsy.—There was acute suppurative pneumonia in the upper lobe of the right lung. In addition there were hemorrhagic cystitis and pyelitis with gangrenous urethritis and ulcerative involvement of the median lobe of the prostate. There was extensive gangrenous ulceration involving tissues about the sacrum and both trochanters, and perforating gangrenous ulcers were seen over both heels. There was a propagating thrombus in the right femoral and iliac vessels and the lower vena cava, distending and occluding them and extending upward into the vena cava and distally into numerous branches.

The peripheral nerves and nerve trunks showed no abnormalities. The brain contained a few areas of focal perivascular atrophy. The spinal cord was badly damaged throughout. The myelin sheaths were degenerated in the posterior and lateral columns and the periphery of the cord, but there were focal areas everywhere in the white matter in which the same process was apparent. The axons and glia were for the most part destroyed in the same areas, leaving a spongelike structure of vacuoles in a reticular network of sparse glia fibers. The recent lesions showed much fat in the vacuolated areas. There was no evidence of gliosis in the lesions.

Case 29.—A man, 26 years of age, was admitted to the hospital complaining of weakness, shortness of breath, palpitation on exertion and loss of appetite with nausea over a period of six months, finally forcing him to give up work. Examination showed a pale, weak, icteric person. The tongue was not atrophic. Over the base of the heart there was a systolic murmur believed to be hemic. The spleen was palpable, and the liver could be palpated at the costal margin. Although the patient felt weak, motor strength was not decreased. The blood tests showed: hemoglobin, 25 per cent; red cells, 1,090,000, and white cells, 8,200. The blood smears revealed marked macrocytosis, anisocytosis and poikilocytosis. There was a definite shift to the right in the nuclei of the neutrophils, some of the cells showing as many as nine distinct lobes. The Wassermann and Kahn reactions were negative. No free hydrochloric acid was shown with the Ewald or histamine tests.

Course.—The patient was given Lilly's liver extract no. 343 on Dec. 2, 1929, three vials a day. There was a 29 per cent reticulocyte count on the fifth day. He was discharged after eighteen days, with a hemoglobin value of 65 per cent and a red cell count of 3,800,000. He walked briskly and felt well, and his appetite was enormous. He was told to eat one-half pound of liver three times a week and to take two vials of liver extract a day. The patient made frequent returns to the outpatient department and was always in a depressed, melancholic or irritable mood. It is doubtful whether the prescribed liver was taken, although he was visited frequently by representatives of the social service department who provided the liver. The hemoglobin was rarely above 70 per cent, and the red cell count rarely was kept above 4,000,000 cells for more than a month at a time, but the neurologic status remained normal. In March 1931, the patient was studied for the first time in our special clinic. The deep reflexes were active and equal, and there was no clonus or Babinski sign. Abdominal reflexes were present. Coor-

dination and sense of position were normal, and there was no ataxia. Vibratory sense was decreased over the lower extremities. There were no objective or subjective sensory disturbances. The tongue was atrophic and the spleen palpable. The blood count at this time was 4,600,000 and the hemoglobin 92 per cent. The smears showed merely a shift to the right in the neutrophils. The patient was given six vials of liver extract a day for three weeks. Then three vials a day were ordered until April 1931. At that time it was decided to give the patient a domestic extract. His condition continued about the same; frequent neurologic examinations revealed no noteworthy change. In February 1932, there was an infection of the upper respiratory tract which reduced the hemoglobin to 45 per cent, the red cell count to 2,200,000 and the white cell count to 8,000, although liver had been taken as directed. At this time he was given 3 cc. of Lederle's liver extract intramuscularly for eleven doses over a period of thirty-nine days. There was a prolonged low reticulocyte response, and at the end of thirty-nine days the hemoglobin was 60 per cent and the red cell count 3,100,000. In May 1932, after taking 1 pound of liver a day in the form of a domestic liver extract, the hemoglobin was 82 per cent and the red cell count 4,140,000. Neurologic changes had occurred which were significant in the light of later findings. The knee and ankle jerks were not elicited, but there were no other abnormalities. It was decided to give the patient light work in the hospital, so that he could be watched more carefully. Intramuscular therapy with Lederle solution liver extract was again instituted. An injection of 3 cc. was given five times in the next eleven days, and once a week thereafter, until the hemoglobin was 90 per cent and the red cell count 4,980,000. When examined on August 17, after he had been seen each week for some time, the patient reported that he had never felt so well; however, the knee jerks and ankle jerks were still absent, even with reenforcement. Although the patient felt better than he had for the past two years and had no subjective symptoms he had lost the knee and ankle jerks during a period when the blood was at a high level.

CASES WHICH SHOWED APPARENT IMPROVEMENT IN NEUROLOGIC STATUS

The following patients were kept on adequate liver therapy for long periods of time and showed what might be interpreted as improvement in some phases of the neurologic syndromes. Proper evaluation shows that the supposed improvement was in reality a progression of signs.

CASE 30.—A white woman, aged 22, was seen for the first time on Jan. 26, 1931. For two years, at frequent intervals, she had felt restless and nervous. In July 1929, she was cut on the right temple, right and left eyebrows and legs in an automobile accident. In two weeks she returned to work. Weakness of the legs and ankles then became evident. There was dull aching in the feet, with some puffiness which was relieved by rest. In November 1929, constipation was marked, and there was bright red blood in the stool, so that a diagnosis of hemorrhoids was made. In the year previous to our first observation there was some disturbance in the sensation of the legs, for the patient felt as if she were walking on "felt." Numbness and tingling were noted together with weakness in the ankles and legs. There had been a loss of 15 pounds (6.8 Kg.), with considerable loss of strength in the last few years.

The pupils reacted to light and in accommodation. The liver and spleen were not palpable, and the tongue was not atrophic. The upper reflexes were hyper-

active and the abdominal reflexes present, but knee and ankle jerks were absent. The Babinski and Romberg responses were both negative. Sense of position and coordination were disturbed in the lower extremities. Vibratory sense was markedly diminished below the tenth dorsal segment and tactile discrimination and sensation were impaired over an area between the knee and the midcalf bilaterally. This examination was checked by several members of the neurologic department.

The Wassermann and Kahn reactions of the blood were negative on two occasions, and the spinal fluid also gave negative reactions to these tests. The urine was normal. There was no free hydrochloric acid according to the Ewald and histamine tests. The hemoglobin was 85 per cent and the red cell count 4,300,000; smears showed none of the typical changes of pernicious anemia except slight hyperchromasia and a few toxic neutrophils.

Course.—A diagnosis of pernicious anemia with degeneration of the posterior column without anemia was made. The patient was ordered to take 1 pound of domestic liver extract a day. She was seen several times in the next three months, and showed no change in neurologic findings except in the development of hyperalgesia over the lower extremities from the knees down. When she was next seen, in April 1932, four months after the first visit, the patellar jerks had returned and were markedly active. All other findings were as before, including the change in deep sensation. This, then, is a definite case of progression in the lateral column, and will be discussed later in the paper. The blood continued to be normal. The patient felt better subjectively and had no complaints.

Case 31.—A woman, aged 70, was first seen by us on Sept. 9, 1931, with the story of two years of ill health, the condition having been diagnosed as pernicious anemia; during this time irregular and insufficient treatment with liver had been given. The disease had begun with tingling and numbness of the hands and feet, but during the past year she had had marked uncertainty in walking and had fallen several times. The patient noted a marked generalized progressive weakness. The red cell count was 3,500,000 and the hemoglobin 78 per cent. According to the histamine test there was no free acid in the gastric contents. Neurologic examination revealed marked impairment of the sense of position in the lower extremities below the knees. The deep reflexes were all reduced and the achilles jerks absent. The Babinski sign was negative; the Romberg sign, positive.

Course.—After taking domestic liver extract, 1 pound a day, the patient became stronger; the red cell count rose to 4,500,000 and the hemoglobin to 89 per cent. In spite of this improvement the defect in vibratory sense ascended to the fifth dorsal level, and spasticity appeared in the lower extremities.

Case 32.—A man, aged 45, entered the clinic on Feb. 13, 1931, complaining of weakness and numbness and tingling in the legs of one year's duration. In the last four months fatigability had become progressive, and he found himself stumbling when walking in the dark. Hyperalgesia of the finger-tips developed. For eight months he had been given arsphenamine intravenously on the assumption that the condition was tabes dorsalis.

Neurologic examination revealed slightly irregular pupils which responded well to light and in accommodation. General muscular strength was diffusely decreased. The gait was spastic, and tone in the lower extremities was increased. The knee jerks were exaggerated and the ankle jerks absent; a bilateral positive Babinski sign was obtained. The Romberg sign was positive, and coordinate movements of the lower extremities were badly performed. Hypalgesia was noted in the lower extremities from the knees down; sense of position was poor in the legs,

and vibratory sensibility was diminished or absent below the level of the tenth dorsal segment. The superficial reflexes were present and lively. The tongue was smooth at the edges, but no other somatic sign could be found. Gastric analysis showed no free hydrochloric acid even after the injection of histamine. The red cell count was 4,500,000 and the hemoglobin 87 per cent. There was a shift of the neutrophils to the right, with anisocytosis. The Wassermann and Kahn reactions were negative in both the blood and the spinal fluid on several occasions.

Course.—The patient was given treatment for pernicious anemia, consisting of domestic extract from 1 pound of liver a day. The tired feeling and ease of fatigue rapidly improved, and the numbness and tingling gradually decreased. In July 1931, an attack of pyelitis with a febrile reaction brought the red cell count down to 3,900,000 and the hemoglobin to 72 per cent, but the blood smears showed little change. Aside from this period the patient's strength remained good, allowing him to return to work; the blood count and hemoglobin remained normal. In spite of improvement in the general condition no change in the objective neurologic findings was noted during the two years of observation, although persistent adequate liver therapy has been maintained.

CASE 33.—A man, aged 58, had general loss of strength, tingling of the fingers and toes and intermittent attacks of yellow coloration of the skin for three years. In the autumn of 1929 he was compelled to give up work, but the correct diagnosis of pernicious anemia was not made until January 1930, after which he was given two blood transfusions and insufficient liver therapy. In September 1931, an unsteady gait developed, and in October mental symptoms appeared in the form of disorientation and confusion. On admission to Billings Hospital on Jan. 11, 1932, he was disoriented and at times irrational. His memory for recent events was poor, but for past events good, and his statements concerning the history were reliable.

Neurologic examination revealed a fine vertical nystagmus and slightly diminished sensibility to pin-prick on the right side. The deep reflexes were all lively and the abdominal reflexes absent. There were a bilateral unsustained ankle clonus and a bilateral Babinski response. Coordination and sense of position were poor in all the extremities, and there was a marked coarse ataxia of the arms and legs. There was a marked generalized asthenia, so that the patient could hardly stand or support his extremities against gravity. The result was that all movements were performed with wide oscillations in range.

The spleen was just palpable. The red cell count was 2,400,000 and the hemoglobin, 50 per cent. There were hyperchromasia and many macrocytes from 13 to 14.8 microns in diameter. Anisocytosis and poikilocytosis were noted, as well as a shift of the neutrophils to the right. Even after the injection of histamine there was no free acid in the gastric contents.

Course.—Three vials of Lilly's liver extract no. 343 were given three times a day, causing a reticulocyte rise to a peak of 11 per cent on the twelfth day. The rise in red cells and hemoglobin was slow, so that three doses of Lilly's solution liver extract were administered intramuscularly. On February 1, the patient became more oriented (the red cell count was 3,400,000 and the hemoglobin 66 per cent). On February 5, the patient was well oriented, the red cell count was 3,800,000 and the hemoglobin was 68 per cent. At this time the patient's strength had so improved that his movements became steadier and smoother, but the finger-to-nose and heel-to-knee tests still showed some ataxia. The Babinski responses and the Romberg sign were positive. The clonus and sensory findings were as before. On April 18, with the red cell count 4,700,000 and the hemoglobin

105 per cent, the sense of position of the legs was evidently more disturbed. The patient walked on a wide base, and the Romberg sign was positive. The gait then was definitely spastic, and the reflexes were markedly exaggerated. On May 15 the red cell count was 4,600,000 and the hemoglobin 104 per cent. The gait was more spastic and the deep reflexes were more exaggerated. This state continued, with the red cell count well over 4,500,000 and the hemoglobin over 100 per cent. During the year of observation the patient consumed the domestic extract of 1 pound of liver each day.

COMMENT

In this patient, with severe symptoms for at least three years, inadequately treated, there developed profound mental and neurologic symptoms engrafted on severe weakness. The mental symptoms quickly disappeared on rejuvenation of the blood; the weakness cleared less rapidly. When strength returned, the striking motor disability disappeared, but the neurologic symptoms and signs remained; in fact, spasticity progressed during a year of adequate therapy. Although the patient now walks and moves well, as contrasted with a previous bedridden state, degeneration of the cord has progressed. This is a striking example of a possible false interpretation of the effect of change in general bodily strength on the neuromuscular status of the patient after therapy.

CASES SHOWING DEFINITE SIGNS OF IMPROVEMENT

CASE 34.—A white woman, 74 years of age, was admitted to the University of Chicago Clinics on Nov. 25, 1929, complaining of a tingling sensation in her hands for several months. Her tongue was sore, and there was a peculiar prickly sensation extending up the spine to the scalp. There was marked irritability. For ten years the patient had had diabetes mellitus, easily controlled by diet.

Examination showed a well nourished woman, pale but not acutely ill. There was loss of vibratory sense from the iliac crests downward with the exception of the right knee joint. The ankle jerks were absent on both sides. The right knee jerk was absent and the left very sluggish. The Babinski reflex was negative, and the abdominal reflexes were absent. There was no definite ataxia. The motor strength was fair. Examination of the blood showed: red cells, 1,900,000; white cells, 3,400; hemoglobin, 48 per cent. Blood platelets were decreased. There were macrocytes present, and the cells showed hyperchromasia. There was a shift of the neutrophils to the right. The Ewald and histamine tests showed no free hydrochloric acid.

Course.—Treatment with Lilly's liver extract was started on Dec. 13, 1929, with four vials a day for three days and then six vials a day, producing a reticulocyte rise of 15.5 per cent on the sixth day. On Jan. 15, 1930, the hemoglobin was 73 per cent and the red cell count 4,100,000, or double that of ten days previously. The patient felt improved subjectively, walked about alertly and was less irritable. She was discharged, with orders to take two vials of liver extract a day. From time to time she was seen, both for treatment of the diabetes mellitus and for a check of the neurologic findings. On Sept. 2, 1932, the hemoglobin was 100 per cent and the red cell count 4,980,000. The reflexes of the upper extremities were active. However, the knee jerks and ankle jerks were absent. On November 7, the blood level was still high. The gait was slightly ataxic, but the upper

extremities were coordinate. The right triceps jerk was reduced, the left was present, and the lower deep reflexes were all absent except the right knee jerk, which was lively, whereas before it had been absent. There was no Babinski reflex or ankle clonus. Sense of vibration was diminished from the iliac crests, but other sensations were normal. Subjectively the patient was feeling very well for her years. Improvement had occurred only in the mental symptoms and peripheral dysesthesia.

CASE 35.—An uncooperative man, aged 56, was first seen on Feb. 12, 1930, after symptoms of from five to six years' duration; during the latter part of this period he had used liver extract irregularly. Neurologically the patient showed decreased knee jerks, absent ankle jerks, a positive Romberg sign and absence of vibratory sense in the legs. He was agitated, had many delusions and was with difficulty prevented from wandering about the ward at all times. On February 20, the red cell count was 800,000 and the hemoglobin 40 per cent. On March 17, he became normal mentally, and the blood picture showed 3,300,000 red cells and 60 per cent hemoglobin.

He was difficult to treat and refused to take the liver regularly. The neurologic symptoms increased; absent knee jerks, exaggerated upper deep reflexes and ataxia were noted, and the positive Romberg sign became worse. On Sept. 1, 1931, he was brought into the hospital again in an irrational state with a red cell count of 1,100,000 and 34 per cent hemoglobin. On September 21, he was rational again, with a red cell count of 3,500,000 and 60 per cent hemoglobin. During the subsequent fifteen months on adequate liver therapy the blood remained normal, but the neurologic defects continued to progress slowly. The irrational episodes were correlated with marked anemia and were alleviated by raising the blood count.

CASE 36.—The patient, a man, aged 62, was first seen on Sept. 20, 1930, with weakness in the legs and knees for six weeks. He had marked numbness and tingling of the toes and fingers. At that time the red cell count was 1,600,000 and the hemoglobin was 49 per cent. There was no free gastric acidity and the tongue was sore. There were slight changes in vibratory sensation in the legs, but no other neurologic findings. With nine vials of Lilly's liver extract a day a reticulocyte response of 23 per cent was obtained on the tenth day. On Nov. 12, 1930, the red cell count was 4,690,000 and the hemoglobin was 92 per cent. On December 9 the red cell count had changed to 5,250,000 and the hemoglobin to 101 per cent. At this time the numbness and tingling disappeared and have remained absent as the blood count has remained up.

CASE 37.—A man, 45 years of age, was admitted to the clinic on Sept. 1, 1932, complaining of a tired feeling and numbness and tingling of the hands and feet over a period of one year. He had been nervous and irritable over the same length of time. In October 1930 the numbness and tingling had spread up the arms to the elbow. Two months later numbness was progressive up to the knees and associated with a stiffness of both upper extremities. He began to feel unsteady on his feet and was never sure that his feet were in contact with the ground.

There were no abnormal physical findings except those of the nervous system. The patient walked on a wide base and was slightly unsteady. There was spasticity of the lower extremities, and the knee jerks and ankle jerks were exaggerated. The Romberg response was positive. Sense of position and coordination were normal and vibratory sense was only slightly reduced. The Babinski reflex was negative. The hemoglobin was 90 per cent and the red cell count 5,010,000. The smears looked normal. There was no free hydrochloric acid according to the Ewald or histamine tests. The Wassermann reactions of the blood and spinal fluid were negative.

Course.—A diagnosis of pernicious anemia was made, and the patient was told to take liver extract from 1 pound of liver daily. Subjectively the patient felt improved. There was still paresthesia in the hands and feet. On the next visit, three months later, neurologic findings were the same, but the patient was feeling so well that he wished to discontinue the liver therapy for the summer. The importance of liver therapy was explained, but he wished a rest. Two months later he returned because he was not feeling well. The symptoms were vague; he tired easily and felt fatigued most of the time. Neurologic findings were as before. The blood was still normal.

This patient, without anemia or a suspicious blood picture, showed evidence of combined degeneration of the cord. Subjective improvement occurred on treatment with domestic liver extract from 1 pound of liver a day. A period of two months without therapy caused a return of the tired feeling and fatigability. Objective neurologic tests remained the same.

COMMENT

A study of case histories is not an adequate method of evaluating a form of treatment, especially when the signs and symptoms which may undergo improvement require considerable skill to elicit. The comparison of findings brought out by one examiner before therapy and another after therapy offers obvious objections; the patient should be observed throughout the period of treatment by the same examiner. In many cases remarkable improvement was reported because of the multiplicity of examiners; furthermore, in the available literature not one neurologist has reported improvement in his cases. In all the cases herein reported the patients were reexamined by us at frequent intervals over a variable but usually adequate total period of time, and assurance was at hand that ambulatory patients were fulfilling therapeutic suggestions.

Weakness is an important symptom of pernicious anemia, depending in degree on the severity of the anemia. Case 37 is a possible exception, since the weakness was unassociated with anemia and was directly improved by liver therapy. However, weakness usually rapidly and often completely recedes when the blood count is brought up to figures approaching normal, and therefore is amenable to liver therapy. Weakness often produces effects which resemble the results of primary damage to the central nervous system. A weak person is ataxic and incoordinate; in fact, with a severe anemia his gait is often worse than that seen in advanced tabes dorsalis or cerebellar disease; he may be unable to walk at all. The muscles become flabby and hypotonic, and the deep reflexes may be markedly decreased. During treatment, as the blood count rises, the strength improves, and simultaneously the supposed neurologic signs and symptoms rapidly regress in a period of time much too short for any anatomic regeneration or physiologic reorganization. Case 33 is

such an example. The rapidity of effect resembles that seen after feeding a depleted animal a single dose of vitamin B_2. Furthermore, as strength increases the patient is able to compensate by voluntary effort for mild defects in his sense of position or changes in muscle tone. Careful examination will show no actual change in objective neurologic signs.

Before evaluating the effects of liver therapy on the spinal cord complications of pernicious anemia, it is necessary to know what clinical changes might be expected from improvement. The terms posterolateral sclerosis and combined degeneration of the cord are indicative of the seat of greatest damage to the spinal cord: the posterior and lateral (particularly posterolateral, wherein lies the pyramidal system) tracts. Other regions of the cord are involved to a less degree. Lesions of the posterior regions of the cord will cause decrease in tone and deep reflexes and disturbance of coordination and position sense. Lesions of the lateral regions will effect an increase in tone and in the deep reflexes, a positive Babinski reflex and changes in sensation referable to damage of the long spinothalamic tracts, while troubles in coordination will be masked by the spasticity.

It can easily be seen that the effects of the involvement of the posterior and lateral columns on muscle tone and deep reflexes are opposite in character. Combinations occur which vary in each case. Assuming that posterior column signs of decreased tone and decreased reflexes could improve, the evidence would be a return of tone and reflex activity to their normal intensity. However, supposing that the posterior column symptoms were unaffected by treatment, but progression occurred so that the lateral tracts became involved, tone and reflex activity would return to normal or become exaggerated. If lateral tract symptoms of hyperreflexia and hypertonia were to improve, the result would be a decrease in those signs exactly as if added damage were to be inflicted on the posterior horns and columns. The syndrome of combined degeneration of the cord is a combination of degeneration of the lateral and the posterior columns, hardly ever quantitatively equal, but varying in degree in each case and frequently associated with successive rather than simultaneous initial involvement. Thus, great errors may be introduced in the evaluation of neurologic signs, mistaking progression of the disease for its improvement. However, the Babinski response on the one hand and the character of the sensory changes on the other will serve to indicate the true state of affairs. If tone and reflexes were to return in a person who had a posterior cord lesion his sense of position and vibratory sensibility should also return (case 30), while in involvement of the lateral tract losses of pain and temperature sense should recede.

In this series of cases we were unable to discover, even in patients who ingested a pound of liver a day for two years, any improvement

in the organic neurologic signs or symptoms (cases 1 to 19, table). Once the rapid improvement in strength was discounted, and if care were observed to avoid falling into the error of interpreting progression as regression, one can apply the same statement to most of the cases reported in the literature. This result is not at all surprising to one familiar with the pathologic findings of combined degeneration of the cord. The entire neuron is destroyed in small foci, often in perivascular areas throughout the cord, but most markedly in the posterior and posterolateral columns. There is no selective demyelinization, but the whole structure is destroyed, including most of the glial stroma. Astrocytic invasion of the damaged area is minimal, so that a status spongiosus is formed. The possibility of such a lesion undergoing improvement is unthinkable, unless, as Suzman and Ungley have suggested, regeneration of central nerve fibers could occur. Gerard and Grinker [15] have shown that even in immature mammals under ideal circumstances regeneration cannot take place. Furthermore, Davidson, on examination of several adequately treated patients with combined degeneration of the cord found no neuronal regeneration, but a proliferation of glia seemed to have been stimulated, causing a glial scar to form in an otherwise spongious tissue.

Collier stated that he had never seen complications referable to the spinal cord develop in a case of pernicious anemia after it had come under observation, and Piney recently reiterated this opinion. They meant that once the anemia has developed, degeneration of the cord either is obvious at the onset or never develops. This statement is somewhat extreme, although one of us (R. R. G. [16]) found that when the clinical disease includes nervous complaints in the original list of symptoms, degeneration of the cord will develop about four times more frequently than in those cases in which nervous complaints develop after the onset. Numerous exceptions to this statement are constantly encountered, and it is known today that there exists no constant relationship between the degree of anemia and the degeneration of the cord. It is likely that as liver therapy prolongs the lives of patients with pernicious anemia, the number of cases of degeneration of the cord will increase.

Notwithstanding the impossibility of improving cord symptoms, liver therapy would be of great advantage if further damage could be prevented or if onset of involvement of the cord could be prevented. Such a prophylactic action of liver cannot be concluded, as Starr did from a series of 4 cases. In our series of cases progression of symptoms and

15. Gerard, R., and Grinker, R. R.: Regenerative Possibilities of the Central Nervous System, Arch. Neurol. & Psychiat. **26**:469 (Sept.) 1931.

16. Grinker, R. R.: Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, Arch. Int. Med. **38**:292 (Sept.) 1926.

signs in the cord occurred in patients under continuous and adequate liver therapy, with blood counts within normal limits (cases 20 to 29). In our cases progression was not more noteworthy in insufficiently treated patients than in those receiving adequate therapy over a long period of time. The factors concerned in progression, like those involved in the etiology of the degeneration of the cord, are not related to the liver intake or to the height of the blood count. Our experience shows that cord symptoms develop rather suddenly and come to a certain maximum rapidly, and then either remain stationary for a long period or slowly progress, no matter what is done for them.

Patients in whom cord symptoms develop before any sign of blood dyscrasia are numerous enough to offer difficulties in diagnosis. Two such cases (30 and 32) are included in this series, and several others have been seen. They show achlorhydria and signs of dorsal, lateral or combined column degeneration. Vague signs are often present in the blood in the form of a shift in the Price-Jones curve or neutrophils of pernicious anemia, but often it is several years before true anemia develops. The public acceptance of the dictum that liver prevents anemia may be responsible for an increasing number of these cases. With liver forming a part of the diet of large groups of the population, neurologic diagnosis of the cause of degeneration of the cord must depend less and less on the presence of anemia and more on the character of the changes in the cord, the achlorhydria and the blood smear.

A further difficulty lies in the differentiation between permanent cord symptoms and peripheral nerve symptoms, from which the patient will recover. The criteria used to separate these two neurologic complications of pernicious anemia are not definite. Using dysesthesia as evidence of damage to the cord, Woltman found that combined degeneration developed in 80 per cent of cases of pernicious anemia. Using other criteria, one of us (R. R. G.) found that only 30 per cent showed this complication. As Hamilton and Nixon have shown, degeneration of the peripheral nerves is not infrequent in pernicious anemia. The usual clinical picture is that of dysesthesia with some hyperalgesia. The skin may become atrophied, smooth and shiny. In more advanced cases objective sensory losses and actual atrophies may appear. The process attacks the distal portions of the extremities, especially the hands. It has a definite relationship to the degree of anemia and is probably due, like the homologous change in peripheral arteriosclerosis, to an anoxemia of the distal nerve fibers. Improvement gradually occurs when the anemia regresses, since peripheral nerve fibers regenerate with ease. Rapidly disappearing dysesthesia is probably due to a functional disturbance before actual degenerative changes have appeared. It is, of course, a question whether disturbances in deep sensation may not be selective according to involvement of the peripheral nerves, as in the

example of postdiphtheritic neuritis of the ataxic type. Some of the rapid sensory restitution reported after liver therapy, if a true finding, may indicate the origin of the disturbances in the peripheral nerves.

Mental symptoms may well be due to focal areas of destruction in the brain, the well known Lichtheim plaques. More often the disorientation and irrational state are due to the anemia alone. Case 35 demonstrated two episodes of severe anemia in the same patient accompanied by mental symptoms. These conditions change quickly when the red cell count approaches 3,000,000. The effect of therapy alone serves to differentiate the organic changes from those due to the anemia.

CONCLUSIONS

1. Liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia.

2. Liver improves the general strength of the patient with combined degeneration of the cord by increasing the number of red cells in the circulating blood or by some obscure direct action. Weakness may closely imitate the effects of damage to the spinal cord.

3. Liver cures the mental symptoms of pernicious anemia, which are usually caused by the anemia.

4. The peripheral nerve complications of this disease, consisting of dysesthesia, atrophic changes in the skin and perhaps other dissociated sensory defects, are alleviated by the recession of the anemia. Such complications are much more frequent than they are usually believed to be.

5. The majority of cases of combined degeneration of the cord develop rapidly at the onset and then progress slowly, no matter what therapy is employed. Gradual progression of signs may be falsely interpreted as signifying improvement.

6. Combined degeneration of the cord develops not infrequently before the anemia and should be diagnosed by the character of the cord syndrome, the achlorhydria, glossitis and blood smear.

7. Liver therapy in pernicious anemia should be controlled by the height of the blood count. Quantities of liver in excess of that necessary to maintain a normal blood level are wasted.

NOTE.—The patients described in this report have been given Lederle solution liver extract intramuscularly since March, 1933, and are being watched for neurologic changes.

CHARACTERISTICS OF THE SYNOVIAL FLUID IN VARIOUS TYPES OF ARTHRITIS

STUDY OF NINETY CASES

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The etiologic diagnosis of arthritis frequently presents many difficulties, and in many cases the cause remains obscure. For that reason, every effort should be made to obtain as much information as possible from the study of the course of the disease and the characteristics of the synovial fluid. During the past two years, we have studied a hundred and twenty samples of synovial fluids from ninety patients with various types of arthritis. We were interested in determining what information of diagnostic value could be obtained from the study of synovial fluid. The types of cases studied are listed in table 1.

METHODS

All the patients were studied while residing in the hospital. With a needle and syringe, fluid was aspirated from the joints, the usual aseptic precautions being taken. The skin was anesthetized with a 2 per cent solution of procaine hydrochloride.

A sample of the aspirated fluid was mixed with sodium oxalate crystals to prevent clotting and examined chemically for the content of total protein, sugar and nonprotein nitrogen. In forty-five cases, blood was withdrawn from a vein simultaneously for comparison of the sugar and nonprotein nitrogen content of the blood and the synovial fluid.

Aspiration was not performed following a period of fasting, so that this factor will require consideration in the interpretation of the comparative results, to be discussed presently.

Total cell counts were done on the synovial fluid immediately after aspiration. Differential cell counts were done according to the supravital technic. Gonococcic complement fixation tests were done on the blood and synovial fluid in a number of cases, and the Wassermann test was likewise done on both the blood and the synovial fluid.

The synovial fluids were cultured for micro-organisms, and in suspected cases of tuberculous arthritis samples of the fluid were injected into guinea-pigs.

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OBSERVATIONS

Gonococcic Arthritis.—In another place we[1] have presented the results of a study of the synovial fluid in gonococcic arthritis, and we include a summary of the findings in this article in order that they may serve as a basis for comparison with other types of arthritis. To repeat briefly, it was found that the synovial fluids from cases of gonococcic arthritis could be divided into two groups, on a basis of the presence or absence of organisms. The results of the study have been included in table 10. On the whole, the average cell count was higher in the infected fluids. The polymorphonuclear leukocytes were more abundant, and the other cells were fewer in number in the infected fluid than in the non-infected samples. The total protein content was increased above the

TABLE 1.—*Types of Cases Studied*

		Number of Cases	Number of Specimens of Synovial Fluids Examined
Gonococcic arthritis		41	53
Rheumatic fever		15	19
Rheumatoid arthritis		16	22
Tuberculous arthritis		5	10
Miscellaneous cases		13	16
Charcot joints	3		
Syphilitic arthritis	2		
Scurvy	1		
Hemolytic streptococcic arthritis	3		
Traumatic arthritis	2		
Myocardial insufficiency	1		
Degenerative arthritis	1		
Total		90	120

normal in both; the nonprotein nitrogen value was the same as that of the blood, and the sugar content varied in three factors: the number of leukocytes in the synovial fluid; the presence of micro-organisms, and the level in the blood at the time, or before, aspiration of the joints. The gonococcic complement fixation test was positive in 86 per cent of the cases in the blood and in 76 per cent of the cases in the synovial fluid. Usually the results of the tests in the synovial fluid and the blood were in agreement. Rarely, the blood serum showed a positive reaction before the synovial fluid.

Acute Rheumatic Fever.—The synovial fluids from fifteen patients with rheumatic fever were studied. Total and differential cell counts

1. (*a*) Myers, Walter K., and Keefer, Chester S.: The Gonococcal Complement Fixation Test in the Blood and Synovial Fluid of Patients with Arthritis, New England J. Med. **211**:101, 1934. (*b*) Myers, W. K.; Keefer, C. S., and Holmes, W. F., Jr.: The Characteristics of Synovial Fluid in Gonococcal Arthritis, J. Clin. Investigation **13**:767, 1934.

were done on nineteen samples of fluid, and the results are recorded in table 2 and summarized in table 10. In all cases, the polymorphonuclear cells predominated, and, as a rule, the higher the total count the greater the relative number of polymorphonuclears. As a rule, the monocytes and clasmatocytes were present in larger numbers in the cases with low total counts. All the fluids were sterile on bacteriologic culture. The results of the chemical examinations of twelve samples of synovial fluid are recorded in table 3 and summarized in table 10. The nonprotein nitrogen value was practically the same as in the blood, whereas the sugar content of the synovial fluid was the same as or higher than

TABLE 2.—*Total and Differential Cell Counts of Synovial Fluid in Rheumatic Fever*

Case Number	Total Cell Count, per C.Mm.	Differential Cell Count, per Cent				
		Polymorphonuclears	Lymphocytes	Monocytes	Clasmatocytes	Eosinophils
41	8,850	70	..	11	19	..
43	13,500	83	4	3	10	..
44	4,250	73	3	6	18	..
46	2,450 R.*	89	2	2	7	..
	10,450 L.	88	7	2	3	..
52	39,500	97	..	..	3	..
53	2,900 R.	97	1	..	2	..
	3,200 L.	78	2	6	14	..
54	26,600	95	..	5	..	..
55	3,550	86	1	7	6	..
56	12,550	95	..	4	1	..
58	34,350	92	3	5	..	..
59	16,850	78	3	11	8	..
60	21,800	96	2	2	..	..
61	22,000	97	2	1	..	..
62	21,500 L.	89	7	3	1	..
	15,900 R.	92	1	4	3	..
63	11,500 R.	91	..	..	9	..
	15,450 L.	98	..	..	2	..

* R indicates that the data are on the right knee and L on the left knee.

that of the blood. This is evidence of a noninfected fluid. The higher values in the synovial fluid can be explained on the basis of the fact that most of the examinations were done several hours after a meal, and it is known from previous work [2] that the fall of the sugar content of the blood precedes that of the synovial fluid.

Rheumatoid Arthritis.—Twenty-three fluids from sixteen patients were studied. The results of the cell counts are recorded in table 4 and summarized in table 10. In most cases the polymorphonuclear cells predominated, but the variations in the number of different cells were wide. This probably depended to some extent on the type of cellular reaction in the synovial cavities at the time of aspiration. All the fluids

2. (*a*) Cajori, F. A.; Crouter, C. Y., and Pemberton, R.: The Physiology of Synovial Fluid, Arch. Int. Med. **37**:92 (Jan.) 1926. (*b*) Allison, N.; Fremont-Smith, F.; Dailey, M. E., and Kennard, M. A.: Comparative Studies Between Synovial Fluid and Plasma, J. Bone & Joint Surg. **8**:758, 1926.

TABLE 3.—*Results of Chemical Examination of Blood and Synovial Fluid in Rheumatic Fever*

Case Number	Total Protein in Joint Fluid, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.		Sugar, Mg. per 100 Cc.		Cells, per C.Mm.
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
44	2.0	26	28	71	74	13,500
45	2.3	37	33	87	125	4,250
47	3.8	35	35	108	121	2,450
52	3.6	32	50	115	130	39,500
53	3.4	25	22	116	146	2,900
	3.4	25	26	116	155	3,200
54	3.0	27	22	79	109	26,600
55	4.3	20	19	90	109	3,550
56	4.6	32	33	143	155	12,550
58	4.7	35	35	123	104	34,350
59	4.1	35	32	84	84	16,850
63	3.9	24	24	78	91	11,500

TABLE 4.—*Total and Differential Cell Counts in Synovial Fluid of Patients with Rheumatoid Arthritis*

Case Number	Total Cell Count, per C.Mm.	Differential Cell Count, per Cent				
		Polymorphonuclears	Lymphocytes	Monocytes	Clasmatocytes	Eosinophils
42	9,875	91	1	4	3	..
45	1,600	84	9	6	1	..
50	20,100	91	5	4	..	..
51	17,400	94	5	1	..	..
	16,900	100	..	..	..	..
75	6,650	3	67	26	4	1
80	14,600	72	19	7	1	1
81	3,400	60	21	2	2	15
82	67,400	21	22	10	57	..
	74,800	16	5	14	65	..
83	43,500	84	6	8	..	2
84	23,200	98	2	..	..	..
85	1,700	26	26	16	32	..
86	39,800	95	1	2	2	..
	28,000	85	6	9	..	..
	25,650	85	8	3	4	..
87	25,400	84	7	2	7	..
	24,350	98	1	..	1	..
88	14,150	77	16	6	1	..
	11,900	85	13	1	1	..
	12,650	85	12	2	1	..
89	12,000	91	4	5	..	..
90	38,700	97	3	..	..	..

TABLE 5.—*Results of Chemical Examination of Blood and Synovial Fluid in Rheumatoid Arthritis*

Case Number	Total Protein in Joint Fluid, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.		Sugar, Mg. per 100 Cc.		Cells, per C.Mm.
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
42	3.8	29	28	129	125	9,875
46	3.7	26	21	85	99	1,600
51	2.4	35	46	76	80	17,400
75	4.2	50	33	77	94	6,650
80	6.1	..	20	74	78	14,600
81	4.5	29	29	101	124	3,400
87	4.8	33	23	92	100	25,400
88	5.1	26	20	89	91	14,150
90	2.3	26	24	111	87	38,700

were sterile. Chemical examinations of the blood and synovial fluid for the nonprotein nitrogen and sugar content, as well as the total protein content of the synovial fluid, were made of nine samples. The results are recorded in table 5 and summarized in table 10. The total protein values varied from 2.3 to 6.1 Gm. per hundred cubic centimeters; the nonprotein nitrogen value was essentially the same in the synovial fluid as in the blood, and the results of the examination for the sugar content were either the same as those in the blood or somewhat higher.

TABLE 6.—*Total and Differential Cell Counts of Synovial Fluid in Tuberculous Arthritis*

Case Number	Total Cell Count, per C.Mm.	Differential Cell Count, per Cent				
		Polymorphonuclears	Lymphocytes	Monocytes	Clasmatocytes	Eosinophils
66	110,000	79	3	11	7	..
76	45,200	89	7	1	1	2
77	13,450	93	..	2	5	..
78	11,600	52	30	16	1	1
	6,500	45	26	26	..	3
79	12,080	75	16	5	4	..
	13,400	61	18	17	4	..
	43,400	93	4	2	1	..
	13,000	56	12	31	1	..
	13,950	86	7	2	5	..

TABLE 7.—*Results of Chemical Examination of Blood and Synovial Fluid in Tuberculous Arthritis*

Case Number	Total Protein in Joint Fluid, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.		Sugar, Mg. per 100 Cc.		Cells, per C.Mm.
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
77	5.5	21	16	102	116	13,450
78	4.3	28	22	74	79	11,600
				102	160	6,500
79	4.6	22	18	79	91	13,950
	4.7	20	22	80	93	13,400

Tuberculous Arthritis.—Synovial fluids from five cases of tuberculous arthritis, proved by the inoculation of guinea-pigs, were studied. The results of the total and differential cell counts are recorded in table 6. The results of the chemical examinations of four samples are recorded in table 7 and summarized in table 10. The total cell counts were between 6,500 and 110,000 per cubic millimeter, and while the differential formula showed no absolutely characteristic features, it was somewhat more common to observe greater numbers of lymphocytes and monocytes than in the other types of arthritis. The chemical examinations revealed nothing strikingly characteristic.

Miscellaneous Types of Arthritis.—The results of the total and differential cell counts of sixteen samples of synovial fluid from thirteen

patients with various disorders of the joints are summarized in table 8. The chemical examinations in four cases are included in tables 9 and 10.

Total Protein of Synovial Fluid.—The values for total protein included the mucin, as it was not removed by precipitation before the determinations were made. In all cases, the total protein value was

TABLE 8.—*Total and Differential Cell Counts of Synovial Fluid in Miscellaneous Cases of Arthritis*

Case Number	Diagnosis	Total Cell Count, per C.Mm.	Differential Cell Count, per Cent			
			Polymorphonuclears	Lymphocytes	Monocytes	Clasmatocytes
47	Traumatic arthritis	4,800	94	3	..	3
48	Charcot's joint	160	42	6	12	40
		140	70	10	20	..
49	Hemolytic streptococcic arthritis	109,500	100	..	..	..
64	Hemolytic streptococcic arthritis	350,000	96	1	1	2
65	Hemolytic streptococcic arthritis	251,000	94	1	..	5
67	Congenital syphilis	6,750	32	51	14	3
68	Syphilitic arthritis	4,500	52	27	7	14
69	Charcot's joint	18,350	91	..	3	6
70	Charcot's joint	275	25	11	19	45
		600	28	32	9	31
71	Traumatic arthritis	3,550	10	2	42	46
72	Myocardial failure	320	24	26	10	38
73	Scurvy	200	20	18	46	16
74	Degenerative arthritis	600	88	8	4	..

TABLE 9.—*Results of Chemical Examination of Blood and Synovial Fluid in Miscellaneous Arthritis*

Case Number	Total Protein in Joint Fluid, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.		Sugar, Mg. per 100 Cc.		Cells, per C.Mm.
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
48 (Charcot)	3.4	26	30	125	139	160
69 (Charcot)	3.8	42	28	103	125	18,350
70 (Charcot)	4.0	32	26	69	87	275
67 (Syphilitic)	3.8	22	24	126	78	6,750

increased above that which is found in normal synovial fluid (chart 1). The lower values were observed in the miscellaneous group and in some of the cases of acute rheumatic fever and rheumatoid arthritis. On the average, the total amount of protein in the synovial fluid was higher in the infected fluids, that is, from persons with gonococcic and tuberculous arthritis. There was no correlation between the total nitrogen content of the fluid and the number of cells or the nonprotein nitrogen content of individual fluids. The amount of protein in the fluid from the joints depended to some extent on the degree and severity of the inflammatory process present.

TABLE 10.—*Summary of Results of Findings in Synovial Fluid in Ninety Cases of Arthritis Compared with Normal Synovial Fluid*

		Differential Cell Count, per Cent					Chemical Examination			
	Total Number of Cells, per C.Mm.	Polymorphonuclears	Lymphocytes	Monocytes	Clasmatocytes	Eosinophils	Total Protein, Gm. per 100 Cc.	Sugar, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Gonococcic Complement Fixation Test
Normal fluid	±50	±5	?	±58	±30	?	.....	.....	15 to 40 Same as Blood	Negative
Gonococcic arthritis										
Infected fluid	7,000 to 158,000	76 to 99	1 to 14	1 to 7	1 to 12	1 to 2	4.6 to 5.9	52 to 99	16 to 38	Positive in
Noninfected fluid	1,600 to 78,000	46 to 100	1 to 12	1 to 32	1 to 22	1 to 2	3.5 to 6.0	38 to 138	16 to 40	74 per cent
Rheumatic fever	2,450 to 34,350	83 to 97	1 to 7	1 to 11	1 to 19	.....	2.0 to 4.7	74 to 155	19 to 35	Negative
Rheumatoid arthritis	1,700 to 74,800	3 to 100	1 to 67	1 to 26	1 to 65	1 to 15	2.4 to 5.1	80 to 124	20 to 46	Negative
Tuberculous arthritis	6,500 to 110,000	59 to 93	3 to 26	2 to 26	1 to 7	1 to 3	4.6 to 5.5	79 to 160	16 to 22	Negative
Miscellaneous										
Charcot's	275 to 18,350	25 to 70	6 to 32	1 to 42	3 to 46	.....	3.4 to 4.0	78 to 139	24 to 30	
Syphilitic	3,200 to 4,550	17 to 52	35 to 51	7 to 32	3 to 16	.....	3.8	78	24	Negative
Scurvy	200	20	18	46	16	.....	.....	.....	.....	
Streptococcus	100,500 to 350,000	94 to 100	1	1	2	.....	.....	.....	.....	
Traumatic	600 to 3,550	10 to 88	2 to 8	4 to 42	0 to 46	.....	.....	.....	.....	
Myocardial failure with effusion in joints	320	24	26	10	38	.....	.....	.....	.....	

Bacteriologic Examinations.—Bacteria were recovered in ten cases of gonococcic arthritis, three cases of hemolytic streptococcic arthritis and five cases of tuberculosis of the joints. These findings were of great assistance in the etiologic diagnosis of the disease. In all other cases, the fluid of the joints was sterile.

Total and Differential Cell Counts.—The total cell counts of the various synovial fluids varied within wide limits. Infected fluids, such as those seen in hemolytic streptococcic infections, contained over 100,000

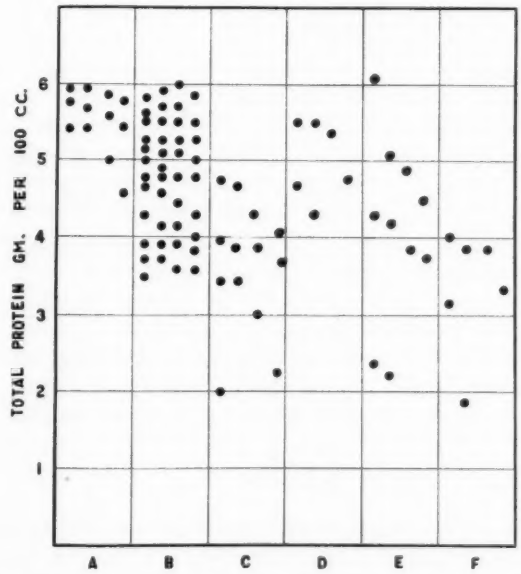

Chart 1.—Total protein content of the synovial fluid in various types of arthritis. Each dot represents the total protein content of the synovial fluid from a patient who showed: *A*, gonococcic arthritis with infected fluid; *B*, gonococcic arthritis with noninfected fluid; *C*, rheumatic fever; *D*, tuberculous arthritis; *E*, rheumatoid arthritis; *F*, miscellaneous arthritides including Charcot joints and syphilitic arthritis.

cells per cubic millimeter, whereas those infected with gonococci seldom contained more than 60,000 per cubic millimeter. In spite of the fact that most of the synovial fluids were noninfected, the vast majority of samples contained less than 40,000 cells. The cases showing the lowest cell counts were those of traumatic arthritis and Charcot joints. In these the count was often less than 1,000 per cubic millimeter. From a study of the total cell counts in the other cases, it was not possible to show

wide variations in the different groups, so that, aside from the cases with very low counts and those with very high counts, the differences were, on the whole, slight.

The differences in the differential counts were more striking than those in the total counts, as the noninfected fluids showed a greater number of monocytes, clasmatocytes and lymphocytes than did the infected fluids. This was particularly evident in the cases of rheumatoid arthritis and in the miscellaneous cases. In the infected fluids the polymorphonuclear cells were usually increased above 80 per cent, with the exception of the tuberculous fluids in which they varied from 46 to 93 per cent.

Nonprotein Nitrogen.—The nonprotein nitrogen content of the synovial fluids varied within the same limits in all groups of cases. The amount could be correlated with the level of nonprotein nitrogen in the blood and not with any other factor, such as the total nitrogen content, cell count or presence or absence of infection. The determination of nonprotein nitrogen, therefore, was of no diagnostic significance.

Sugar Content of Synovial Fluid.—The sugar content of the synovial fluids is shown in chart 2. The data show that the sugar content varied within the same range as the normal value for blood sugar without fasting, but in addition there were a number of instances in which the sugar content of the synovial fluid was below 70 mg. per hundred cubic centimeters. On further analysis, it was found that the amount of sugar in the synovial fluids in all groups of cases depended on three factors: (1) the level in the blood at the time fluid was aspirated from the joint; (2) the number of leukocytes, and (3) the presence of microorganisms.

In some cases, the sugar level of the synovial fluid per hundred cubic centimeters was higher than that of the blood. This can be explained on the basis of the fact that the fluid was not aspirated after the patient had fasted, but frequently several hours after a meal, and it is known that the blood sugar level declines after a meal sooner than the synovial fluid sugar does. It is a matter of importance, then, to interpret the level of the sugar of the synovial fluid as normal, increased or decreased only when one knows the level of the blood sugar and the time in relation to meals that aspiration was performed.

It was found, further, that the level of the sugar of the synovial fluid could be correlated to some extent with the number of cells in the synovial fluid and the presence or absence of infection. The relation between the number of cells and the sugar content of the infected and noninfected fluids is shown in chart 2. Generally speaking, the presence of micro-organisms and a high cell count were accompanied by a smaller amount of sugar in the synovial fluid. But, as the noninfected fluids with a high cell count also showed low values for sugar in the synovial

fluid, it was obvious that both the cell content and the presence of microorganisms were of significance in determining the level of the sugar of the synovial fluid. A low sugar content, then, did not always indicate infected fluid.

Gonococcic Complement Fixation Test.—The results of the gonococcal complement fixation test of the blood serum and synovial fluid of patients with various types of arthritis were reported elsewhere.[18] Forty-eight samples of synovial fluid from twenty-seven patients with gonococcic arthritis were examined. The reaction was positive in thirty-one specimens of synovial fluids, doubtful in one and negative in sixteen. The reactions of the blood serum and synovial fluid, simultaneously

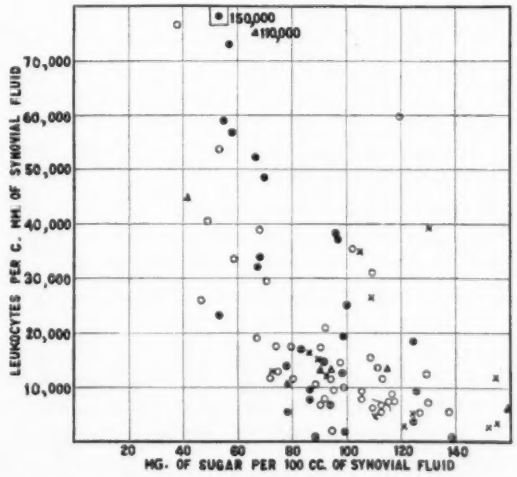

Chart 2.—Total cell counts and sugar content of synovial fluid. Each symbol represents the sugar content per hundred cubic centimeters of synovial fluid from a patient with: dot, gonococcic arthritis with infected fluid; circle, gonococcic arthritis with noninfected fluid; triangle, tuberculous arthritis; cross, rheumatic fever; cross within circle, rheumatoid arthritis, and dot within circle, miscellaneous arthritides.

collected, were identical except in six instances. The reaction of the synovial fluid was negative on four occasions when that of the blood serum was doubtful or positive. In one case, there was a doubtful gonococcic complement fixation reaction of the synovial fluid in association with a positive reaction in the blood serum, and another showed a positive reaction of the synovial fluid with an associated doubtful reaction of the blood serum. In three patients it was possible to observe the change of the reaction in the blood serum and synovial fluid from

negative to positive. The blood serum showed a positive gonococcic complement fixation reaction before the synovial fluid. In three patients, both the blood serum and the synovial fluid gave negative reactions early in the course of the disease when gonococci were recovered from the synovial fluid. The reaction was positive in six specimens of synovial fluid from four other patients with fluid infected by the gonococcus.

Fourteen specimens from twelve patients with rheumatic fever were likewise examined. One from a patient without evidence of gonococcic infection gave a positive reaction. On repeated examination the fluid gave a negative reaction. Sixteen specimens from ten patients with various other disorders of the joints not due to the presence of the gonococcus gave negative gonococcic complement fixation reactions.

TABLE 11.—*Results of the Wassermann Test in the Synovial Fluids from Sixty Cases of Arthritis*

		Fluids				
	Number of Patients	Number of Specimens	Number Plus	Number ±	Number Minus	Number Disagreeing with Blood Serums
Gonococcic arthritis	29	49	1	0	48	3
Rheumatic fever	12	14	0	0	14	0
Rheumatoid arthritis	10	16	0	0	16	0
Syphilitic arthritis	2	4	3	1	0	1
Charcot joints	3	4	0	2	2	2
Miscellaneous	4	6	0	0	6	0
Total	60	93	4	3	86	6

Wassermann Reaction.—The results of the Wassermann test of ninety-three specimens of synovial fluid from sixty patients are shown in table 11. The reactions of both the blood serum and the synovial fluid, simultaneously collected, were negative on eighty-four occasions. Four specimens of synovial fluid from two patients with syphilitic arthritis were examined. The blood serum and synovial fluid were positive on three occasions. Once the reaction of the blood serum was positive when that of the synovial fluid was doubtful. Two patients with Charcot joints due to tabes dorsalis were found to give a positive reaction in the blood serum and a doubtful reaction in the synovial fluid. The synovial fluids from two patients with gonococcic arthritis gave negative Wassermann reactions at the time that the reaction of the blood was positive. In one other patient with gonococcic arthritis the reaction of the synovial fluid was positive when that of the blood serum was negative.

COMMENT

From the data presented we now return to the question we set out to answer, namely: What information of diagnostic value may be obtained

from a study of the synovial fluid in patients with arthritis? Before discussing this question in the light of our material, it is necessary to review the information that exists regarding normal synovial fluid in order to compare the various characteristics of both normal and abnormal synovial fluids.

Under usual circumstances the amount of synovial fluid present in any of the joints is so small that its examination during life is unpractical. Small amounts of fluid have been obtained by various observers [3] during surgical procedures or after death. The results have been summarized by Forkner,[4] who stated that the fluid usually consists of a few cubic centimeters of thick gelatinous material, containing from none to 50 cells per cubic millimeter, chiefly macrophages and small amounts of protein and mucin. It is known, however, from the recent observations of Bauer, Bennett, Marble and Clafton [5] and Bauer, Bennett and Short [6] on the synovial fluid from the normal joints of young beef cattle, that normal synovial fluid consists of a transudation of noncolloidal electrolytes and small amounts of protein from the blood plasma, together with a small amount of mucin. The approximate total protein content of this fluid was calculated to be 680 mg. or 0.68 per cent per hundred cubic centimeters. The nucleated cells varied between 103 and 165 per cubic millimeter. The presence of red blood cells was considered to be the result of trauma. From the recent experiments of Vaubel,[7] it is now proved that mucin is formed by the synovial cells grown in tissue culture.

Bearing these facts in mind, then, it is possible from the examination of synovial fluids in disease to determine in what respect they differ from the normal.

An increase in the amount of synovial fluid may be the result of transudation or exudation resulting from inflammation. Transudates into the cavities of the joints are observed under the same circumstances as they appear in other serous sacs, that is, with increased venous pressure, decrease of plasma protein or obstruction to lymphatic drainage. Thus, one finds effusions into the joints in cases of con-

3. Key, J. A.: Cytology of Synovial Fluid in Normal Joints, Anat. Rec. **40**: 193, 1928.

4. Forkner, Claude: The Synovial Fluid in Health and Disease with Special Reference to Arthritis, J. Lab. & Clin. Med. **15**:1187 (Sept.) 1930.

5. Bauer, W.; Bennett, G.; Marble, A., and Clafton, D.: Observations on Normal Synovial Fluid of Cattle: I. The Cellular Constituents and Nitrogen Content, J. Exper. Med. **52**:835 (Dec.) 1930.

6. Bauer, W.; Bennett, G. A., and Short, C. L.: Speculations on the Etiology of Rheumatoid Arthritis, New England J. Med. **208**:1035 (May 18) 1933.

7. Vaubel, E.: The Form and Function of Synovial Cells in Tissue Culture: II. The Production of Mucin, J. Exper. Med. **58**:85, 1933.

gestive heart failure with edema of the extremities, in some cases with nephrotic edema or in thrombophlebitis of the femoral vein. Under these circumstances, the fluid has a low protein and cellular content. In the one case we studied, the cell count was 320 per cubic millimeter and clasmatocytes, monocytes and lymphocytes predominated. The protein content was low, 1.8 Gm. per hundred cubic centimeters, and the nonprotein nitrogen content was increased as it was in the blood. From the literature, summarized by Forkner,[4] it was stated that transudates were usually transparent, with a specific gravity varying from 1.008 to 1.018. The cells varied from 0 to 50, and were composed mostly of macrophages and mesothelial cells; the protein content was low. The diagnosis of a transudate is justifiable, then, when the synovial fluid has the characteristics just mentioned, or when a synovial effusion occurs in the presence of a disease in which there is transudation of fluid into the other tissues of the body.

When there is an inflammatory lesion of the synovial membrane with an effusion into the cavity of the joint, the characteristics of the fluid are different from normal synovial fluids or from transudates. It is this group of conditions that we studied, and the diagnostic significance of the changes may now be discussed.

From our observations it was plain that the most helpful examination in establishing an etiologic diagnosis of arthritis was the isolation of pathogenic micro-organisms from the synovial fluid. This was especially true in the cases of gonococcic, hemolytic streptococcic and tuberculous arthritis. In all other cases the synovial fluid was sterile.

Cytologic examinations of synovial fluid revealed the fact that during the course of an acute inflammatory lesion of the synovial membrane, the total cell count was increased and polymorphonuclear cells predominated. When the fluids were infected, the cells were commonly all polymorphonuclear. When they were not infected, the lymphocytes, monocytes and clasmatocytes were increased, and comprised between 10 and 60 per cent of the total number of cells. These changes are similar to those found in other effusions of the serous sacs, when the cytology of infected and noninfected fluids is studied.[8] The presence, then, of a cellular reaction in the synovial fluid in which polymorphonuclear cells predominate is evidence of an infected fluid. In the case of tuberculous arthritis, this is not necessarily true, as the polymorphonuclear cells may not predominate in all cases. A low cell count with a high percentage of macrophages and clasmatocytes indicates a noninfected fluid.

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8. Scott, T. F. M., and Finland, M.: The Cytology of Pleural Effusions in Pneumonia Studied with a Supravital Technique, Am. J. M. Sc. **188**:322, 1934.

The gonococcic complement fixation test was of distinct value in the etiologic diagnosis of gonococcic arthritis. This was particularly true in a few patients who had no signs of an active genital infection at the time of the arthritis, but who had a history of a previous infection. This was of interest in view of the previous observation of Forkner,[9] who found gonococci in the lymph nodes of a patient with chronic arthritis eight years after a genital infection, with no active localized genital infection at the time of examination. In our experience, the test was positive in 74 per cent of the synovial fluids examined. These results are in accord with the observations of others.[10] When the blood serum and synovial fluid were examined simultaneously, it was found that the results of the test were in agreement. Occasionally, the blood serum showed a positive reaction before the synovial fluid. In no case was a positive reaction found in the synovial fluid and a negative reaction in the blood, although the results were not necessarily of the same intensity. In view of the negative results in other types of arthritis and the rare occurrence of falsely positive reactions, the test was of assistance in the diagnosis of gonococcic arthritis.

The Wassermann reaction of the synovial fluid provided positive information in the rare cases of syphilitic arthritis. In these cases it is usually positive in both the blood and the synovial fluid, whereas, in the cases of Charcot joints in tabes dorsalis, the reaction may be positive in the blood and negative in the synovial fluid. Since gonococcic and syphilitic infections frequently coexist, the rôle of both infections may be difficult to interpret as far as the arthritis is concerned. However, the presence of a positive Wassermann reaction in the blood and synovial fluid, together with the type of cellular reaction which is characterized by an increase in the number of lymphocytes, monocytes and clasmatocytes, is highly suggestive of active syphilitic arthritis.

The nonprotein nitrogen content of the synovial fluid was of no diagnostic significance in discriminating infected from noninfected fluids or transudates from exudates. The values were the same in both the blood and the synovial fluid, indicating a transudation of the electrolytes from the blood plasma into the synovial cavity.

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9. Forkner, C.: Material from Lymph Nodes: III. Gonococci from Lymphoid Tissue in a Case of Chronic Infectious Arthritis, Bull. Johns Hopkins Hosp. **32**:257 (Oct.) 1928.

10. Holbøll, S. A.: Gonorrheal Arthritis, Particularly with Regard to the Complement Fixation Reaction for Gonorrhea, Hospitalstid. **73**:18 (Jan. 2) 1930. Blix, A. S.: The Complement Fixation Reaction in Gonorrhea, Acta med. Scandinav. (supp.) **50**:332, 1932. Green, F.: Complement Fixation in Gonorrheal Arthritis, Canad. M. A. J. **28**:289 (March) 1933. Kling, D. H., and Pincus, J.: The Gonococcus Complement Fixation Test in Synovial Fluid, J. Lab. & Clin. Med. **17**:39 (Oct.) 1931.

We said previously that normal synovial fluid and transudates into the synovial cavities contain only small amounts of protein. In the cases reported, the total protein content was increased above normal in both the infected and the noninfected fluids from patients with gonococcic arthritis, rheumatoid arthritis, acute rheumatic fever and tuberculous arthritis and in the miscellaneous group of cases. The presence, therefore, of an increased amount of protein in the synovial fluid indicated only an exudate and not the actual presence of infection.

It has been stated that a low sugar content of the synovial fluid is indicative of an infection of the joints,[11] although Pemberton [12] pointed out that the sugar level may be low in noninfected fluids with a high cellular content. We found that both of these factors were significant and that the level of the blood sugar was also of importance in interpreting synovial fluid values. It was not possible from a sugar determination alone to discover whether or not infection was present.

SUMMARY AND CONCLUSIONS

One hundred and twenty samples of synovial fluid from ninety patients with various types of arthritis were studied to determine the diagnostic significance of the various biologic and chemical characteristics of the fluid.

1. The bacteriologic examination of the fluids yielded information of the greatest value in the etiologic diagnosis of arthritis. Inoculation of guinea-pigs with the synovial fluid was helpful in the diagnosis of tuberculous arthritis.

2. The results of the gonococcic complement fixation and Wassermann tests of the blood and synovial fluids were in agreement. Both tests were of distinct aid in the etiologic diagnosis of disease of the joints.

3. The total cell count of the synovial fluid was increased in all the types of arthritis studied. It was highest in the infected fluids and lowest in the cases of Charcot joints and traumatic arthritis. Most noninfected fluids contained less than 40,000 cells per cubic millimeter.

4. When the synovial fluid was infected with micro-organisms, the polymorphonuclear cells were greatly increased, from 86 to 100 per cent, and the lymphocytes, monocytes and clasmatocytes were few in number. In tuberculosis of the joints, the polymorphonuclear count varied from 46 to 93 per cent, and the lymphocytes and monocytes were increased.

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11. Allison, Fremont-Smith, Dailey and Kenard,[2b] Key.[3]

12. Pemberton, R. A.: Arthritis and Rheumatoid Condition, Philadelphia, Lea & Febiger, 1929, p. 129.

5. The percentages of lymphocytes, clasmatocytes and monocytes were always higher in the noninfected fluids than in the infected fluids. The presence of a low cell count with an increase in the monocytes, lymphocytes and clasmatocytes was an indication of a noninfected fluid.

6. The chemical examination of the fluids yielded no information of diagnostic value in discriminating between infected and noninfected fluids. The nonprotein nitrogen of both the infected and the noninfected synovial fluids was the same as that of the blood. The sugar content varied with the presence of organisms, the number of cells and the level of the sugar in the blood. A low sugar content did not always mean an infected fluid. The total protein value of the synovial fluid was increased in both groups, and indicated only an inflammatory reaction.

7. Aside from the bacteriologic, cytologic and serologic examinations of the synovial fluid, other tests yielded little information of diagnostic value.

CALORIGENIC ACTION OF SINGLE LARGE DOSES OF DESICCATED HOG THYROID

COMPARISON WITH THE ACTION OF THYROXINE GIVEN ORALLY AND INTRAVENOUSLY

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Several reports have recently been made from this clinic concerning the effects of administering thyroxine in various forms orally and intravenously in an alkaline solution.[1] These observations have shown that single doses of from 10 to 100 mg. of pure thyroxine administered by mouth or duodenum do not have a demonstrable effect on the basal metabolism of patients with myxedema, whereas the oral administration of single large doses of monosodium thyroxine and thyroxine in alkaline solution causes increases in the basal metabolism of 22 and 63 per cent, respectively, as great on the average as the increase produced by the intravenous injection of an alkaline solution. It seemed important to determine the effect of single large doses of desiccated thyroid of the same iodine content for comparison with these data. We have previously

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1. (*a*) Thompson, W. O.; Thompson, P. K., and Dickie, L. F. N.: Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine: Comparison of Their Effects When Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution, Arch. Int. Med. **52**:576 (Oct.) 1933. (*b*) Thompson, W. O.; Thompson, P. K.; Dickie, L. F. N., and Alper, J. M.: Effect of Alkali on the Absorption of Thyroxine from the Gastro-Intestinal Tract, ibid. **52**:809 (Nov.) 1933. (*c*) Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III; Alper, J. M., and Dickie, L. F. N.: The Effect of Various Compounds of Thyroxine on the Basal Metabolism, Endocrinology **18**: 228, 1934. (*d*) Thompson, W. O.; Thompson, P. K.; Dickie, L. F. N., and Taylor, S. G. III: The Iodine in the Thyroid Gland, West. J. Surg. **41**:431 (Aug.) 1933. (*e*) Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III; and Dickie, L. F. N.: Oral and Duodenal Administration of Single Large Doses of Pure Thyroxine: Comparison of Calorigenic Effects with Those of Monosodium Thyroxine and Thyroxine in Alkaline Solution, Arch. Int. Med. **54**:818 (Nov.) 1934.

reported observations which suggest that the oral administration of desiccated thyroid and the intravenous injection of thyroxine in doses which contain the same total amounts of iodine produce equal increases in the basal metabolism, when the comparison is made on the basis of the quantities of the two substances that have to be administered every day in order to hold the basal metabolism of patients with myxedema at the normal level.[2]

METHOD

Five patients with myxedema[3] were used for this study, and in four of them the effects of giving thyroxine in various ways have also been determined. In patients 1, 3 and 5 the myxedema was spontaneous; in the second patient it followed a subtotal thyroidectomy for exophthalmic goiter, and in the fourth patient, a subtotal thyroidectomy for a nontoxic nodular goiter. Various parts of the data on the first three patients have been published, as they were collected[4] to illustrate other points.

The desiccated thyroid was hog thyroid (Wilson's) containing 0.23 per cent iodine and was used in the form of 1 grain (0.065 Gm.) tablets. All of the thyroid was from one lot except that given to the fifth patient. Since the mode of administration, particularly with reference to food, may be important, these details are incorporated in the legends of the charts.

For all the patients, curves are recorded showing the complete effect on the basal metabolism of each administration of desiccated thyroid or of thyroxine. These curves not only show the amount of increase in the basal metabolism, but make it possible to calculate roughly, by a method previously described,[5] the total number of excess calories produced.

The monosodium salt of synthetic thyroxine was administered in the form of tablets each of which contained 1.03 mg. of the salt.

The Sanborn-Benedict and Benedict-Roth machines were used in making the basal metabolism determinations, and Aub-DuBois standards were used in the calculations.

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2. Thompson, W. O.; McLellan, L. L.; Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: The Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, J. Clin. Investigation **12**:235 (Jan.) 1933.

3. All of the data on the fifth patient and most of the data on the fourth patient were collected at the Cook County Hospital; the remainder, at the Rush Medical College and at the Presbyterian Hospital. Dr. Frederick Tice and Dr. Karl A. Meyer allowed us to collect the data at the Cook County Hospital.

4. Thompson, W. O.; Alper, J. M.; Thompson, P. K., and Dickie, L. F. N.: The Effect of Diiodotyrosine on the Basal Metabolism in Myxedema, J. Clin. Investigation **13**:29, 1934; footnote.[1b]

5. (*a*) Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenetic Action of Thyroxine at Different Levels of Basal Metabolism in Myxedema, J. Clin. Investigation **7**:437 (Aug.) 1929. (*b*) Thompson, McLellan, Thompson and Dickie.[2]

DATA

The data are recorded in charts 1 to 5 and summarized in tables 1 and 2. In order to facilitate comparison, the effects of all the doses of desiccated thyroid and of thyroxine have been calculated in terms of 6.5 mg. of iodine by the method indicated in the footnotes to the tables. It may be noted that the effect of a given dose of desiccated thyroid varied somewhat from patient to patient. Thus, by calculation, the smallest absolute increase in basal metabolism for doses containing 6.5 mg. of iodine was 15 points (from minus 26 to minus 11 per cent) and the greatest, 28 points (from minus 39 to minus 11 per cent), while the average increase was 22 points (from minus 37 to minus 15 per cent). The number of excess calories produced by the same

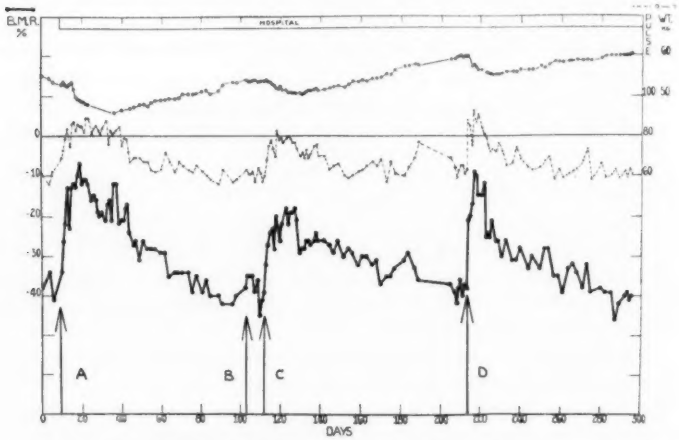

Chart 1.—Comparison of effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs. M. M., height, 159 cm., age, 58). *A* indicates intravenous administration of 10 mg. of synthetic thyroxine in alkaline solution; *B*, oral administration of 10 mg. of synthetic thyroxine in distilled water; *C*, oral administration of 10 mg. of synthetic thyroxine in alkaline solution; *D*, oral administration of 2.75 Gm. of desiccated thyroid. Details of the three administrations of thyroxine have been published.[1b] The dose of 2.75 Gm. (42.4 grains) of desiccated thyroid was given at 11:20 a. m. on April 30, 1933, the patient having had no food since 6 o'clock the night before. A total of 250 cc. of distilled water was used to wash down the tablets.

dose varied from 3,260 in the third patient to 9,795 in the fourth patient. The average number was 7,405.

In the first four patients the effect of giving thyroxine intravenously in alkaline solution was also observed. In the first patient the increase in basal metabolism produced by the oral administration of 2.75 Gm.

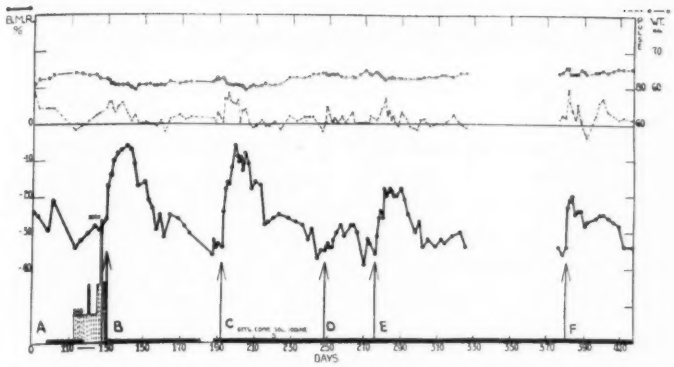

Chart 2.—Comparison of the effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs. A. R., height, 160 cm.; age, 33). The treatment was as follows: intravenous administration (*A*) of diiodotyrosine (in milligrams), (*B*) of 7.5 mg. of synthetic thyroxine in alkaline solution and (*C*) of 7.5 mg. of natural thyroxine in alkaline solution; oral administration (*D*) of 7.5 mg. of synthetic thyroxine in the form of the monosodium salt, (*E*) of 7.5 mg. of synthetic thyroxine in alkaline solution and (*F*) of 2.05 Gm. of desiccated thyroid. Details of the various administrations of thyroxine have been published.[1b] The dose of 2.05 Gm. (31.7 grains) of desiccated thyroid was given at 4:20 p. m. on April 24, 1933, the patient having had lunch about four hours before. A total of 250 cc. of distilled water was used to wash down the tablets.

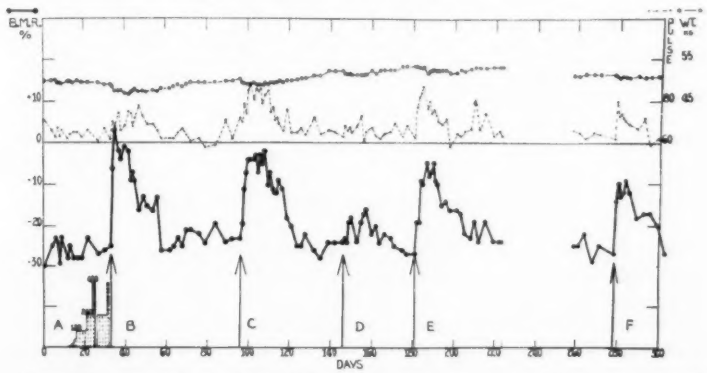

Chart 3.—Comparison of the effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs. M. K., height, 152 cm.; age, 36). Treatment was as follows: intravenous administration (*A*) of diiodotyrosine in milligrams, (*B*) of 10 mg. of synthetic thyroxine in alkaline solution and (*C*) of 10 mg., of natural thyroxine alkaline solution; oral administration (*D*) of 10 mg. of synthetic thyroxine in form of the monosodium salt, (*E*) of 10 mg. of synthetic thyroxine in alkaline solution and (*F*) of 2.75 Gm. of desiccated thyroid. Details of the various administrations of thyroxine have been published.[1b] The dose of 2.75 Gm. of desiccated thyroid was given at 11 a. m. on April 10, 1933, the patient having fasted since 6 o'clock the night before. A total of 250 cc. of distilled water was used to wash down the tablets.

(42.4 grains) of desiccated thyroid containing 6.3 mg. of iodine (from minus 39 to minus 12 per cent) was about the same as that produced by the intravenous administration of 10 mg. of thyroxine containing 6.5 mg. of iodine (from minus 40 to minus 11 per cent). In patients 2, 3 and 4 the increases produced by desiccated thyroid were less than those produced by giving thyroxine intravenously, the increases being, respectively, 59, 68 and 84 per cent as great. In other words, in some patients the effect of a single large dose of desiccated thyroid may be nearly twice as great as in others when the comparison is made with

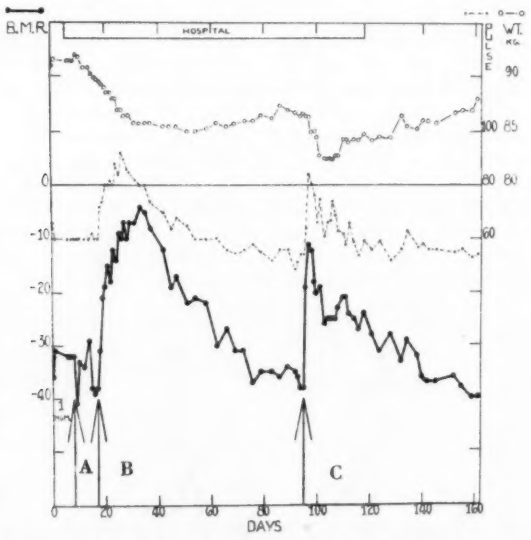

Chart 4.—Comparison of effects of oral administration of a single large dose of desiccated thyroid with those of intravenous administration of a single large dose of thyroxine in a patient with myxedema (Mrs. C. F., height, 163 cm.; age, 44). An intravenous injection of 1 mg. of synthetic thyroxine (*A*) was made at 4:25 p. m. on Feb. 2, 1933, the thyroxine being dissolved with the aid of potassium hydroxide. An intravenous injection of 10 mg. of synthetic thyroxine (*B*) was made at 4:18 p. m. on February 11, the thyroxine being dissolved by the addition of 4 drops of a 10 per cent solution of potassium hydroxide to its suspension in distilled water. It was sterilized for injection by placing the test tube which contained it in a beaker of boiling water for twenty minutes. A dose of 2.75 Gm. of desiccated thyroid (*C*) was administered at 2:45 p. m. on April 30, the patient having had dinner at 11:20 a. m. A total of 500 cc. of distilled water was used to wash down the tablets.

the effect of an intravenous dose of thyroxine containing the same amount of iodine. The increase from desiccated thyroid in all four

patients was 76 per cent as great on the average as that produced by thyroxine given intravenously.

In the first three patients we have also observed the effects of giving thyroxine by mouth in a solution of sodium hydroxide and in the form of its monosodium salt (tablets). In the first patient the increase in basal metabolism produced by giving thyroxine in alkaline solution was less than that produced by giving a dose of desiccated thyroid containing about the same amount of iodine, but in the second and third patients the effect was greater. On the average, for quantities containing 6.5 mg. of iodine, the thyroxine given by mouth

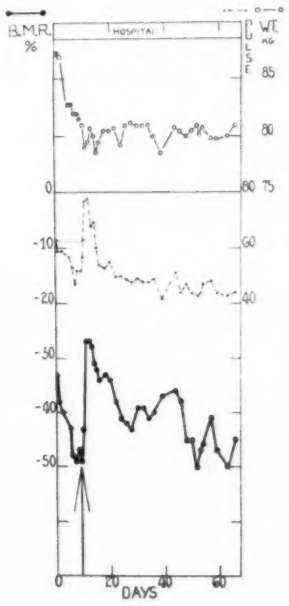

Chart 5.—The effect of oral administration of a single large dose (2.75 Gm.) of desiccated thyroid to a patient with myxedema (Mr. G. H., height, 194 cm.; age, 54). The administration was made at 5 p. m. on May 12, 1933, shortly after supper, a total of 500 cc. of distilled water being used to wash down the tablets.

in an alkaline solution produced an increase in basal metabolism of from minus 34 to minus 13 per cent in the three patients, and desiccated thyroid caused an increase of from minus 33 to minus 13 per cent, while thyroxine given intravenously in an alkaline solution to the same three patients produced an increase of from minus 32 to minus 5 per cent. Thus the changes produced by the oral administration of desiccated thyroid and by an alkaline solution of thyroxine were almost the

TABLE 1.—*Comparison of Effects on Basal Metabolism of Single Large Doses of Desiccated Thyroid with Those of Thyroxine Given Both Orally and Intravenously*

Patient	Medication	Total Iodine Content of Substance Used, Mg.	Basal Metabolic Rate Before Medication, per Cent of Normal	Level to Which Basal Metabolic Rate Rose, per Cent of Normal	Change in Basal Metabolic Rate, Points	Time Required for Maximum Change in Basal Metabolic Rate, Days	Length of Time Basal Metabolic Rate Was Affected, Days	Time Occupied by Descending Portion of Metabolism Curve, Days	Number of Excess Calories Produced	Change in Terms of Response to Intravenous Injection of 10 Mg. of Thyroxine in Alkaline Solution*	
										On Basis of Increase in Basal Metabolic, per Cent	On Basis of Excess Calories Produced, per Cent
Mrs. M. M.	10 mg. of synthetic thyroxine in alkaline solution, intravenously	6.5	—40	—11	29	9	80	66	14,860	100	100
	10 mg. of pure synthetic thyroxine suspended in distilled water, by mouth	6.5	—40	—35	5	1	8	5	310	17	2
	10 mg. of synthetic thyroxine in alkaline solution, by mouth	6.5	—40	—19	21	6	95	80	12,050	72	81
	2.75 Gm. (42.4 grains) of desiccated thyroid (tablets), by mouth	6.3	—39	—12	27	4	69	64	9,005		
	Calculated effect of 2.83 Gm.† desiccated thyroid by mouth	6.5	—39	—11	28	..	..	..	9,265	97	62
Mrs. A. R.	7.5 mg. of synthetic thyroxine in alkaline solution, intravenously	4.9	—30	— 7	23	6	45	32	6,910		
	7.5 mg. of natural thyroxine in alkaline solution, intravenously	4.9	—34	— 9	25	7	53	41	9,000		
	Average effect of 7.5 mg. of thyroxine in alkaline solution, intravenously	4.9	—32	— 8	24	6	49	37	7,955		
	Calculated effect of 10 mg. of thyroxine‡ in alkaline solution, intravenously	6.5	—32	0	32	..	..	..	10,605	100	100
	7.5 mg. of synthetic thyroxine in form of its monosodium salt (tablets), by mouth	4.9	—36	—29	7	6	27	10	1,825		
	Calculated effect of 10 mg. of synthetic thyroxine in form of its monosodium salt, by mouth	6.5	—36	—27	9	..	..	..	2,435	28	23
	7.5 mg. of synthetic thyroxine in alkaline solution, by mouth	4.9	—35	—19	16	5	42	28	4,990		
	Calculated effect of 10 mg. of synthetic thyroxine in alkaline solution, by mouth	6.5	—35	—14	21	..	..	..	6,655	66	63

	2.05 Gm. (31.7 grains) of desiccated thyroid (tablets), by mouth	4.7	−35	−21	14	2	34	31	4,385		
	Calculated effect of 2.83 Gm. of desiccated thyroid, by mouth	6.5	−35	−16	19	..	..	..	6,055	59	57
Mrs. M. K.	10 mg. of synthetic thyroxine in alkaline solution, intravenously	6.5	−26	− 1	25	2	29	22	5,135		
	10 mg. of natural thyroxine in alkaline solution, intravenously	6.5	− 23	− 4	19	4	29	17	4,300		
	Average effect of 10 mg. of thyroxine in alkaline solution, intravenously	6.5	−25	− 3	22	3	29	20	4,720	100	100
	10 mg. of synthetic thyroxine in form of its monosodium salt (tablets), by mouth	6.5	−25	−19	6	3	25	14	1,305	27	28
	10 mg. of synthetic thyroxine in alkaline solution, by mouth	6.5	−26	− 6	20	6	33	24	4,315	91	91
	2.75 Gm. (42.4 grains) of desiccated thyroid (tablets), by mouth	6.3	−26	−11	15	2	33	26	3,170		
	Calculated effect of 2.83 Gm. of desiccated thyroid, by mouth	6.5	−26	−11	15	..	..	..	3,260	68	69
Mrs. C. F.	10 mg. of synthetic thyroxine in alkaline solution (potassium hydroxide), intravenously	6.5	−38	− 6	32	10	77	59	19,410	100	100
	2.75 Gm. (42.4 grains) of desiccated thyroid (tablets), by mouth	6.3	−38	−12	26	2	60	57	9,520		
	Calculated effect of 2.83 Gm. of desiccated thyroid, by mouth	6.5	− 38	−11	27	..	..	..	9,795	84	50
Mr. G. H.	2.75 Gm. (42.4 grains) of desiccated thyroid (tablets), by mouth	6.3	−48	−27	21	2	47	44	8,410		
	Calculated effect of 2.83 Gm. of desiccated thyroid, by mouth	6.5	−48	−26	22	..	..	..	8,655		

* For each patient the figures in the first column under this heading have been calculated by dividing the number of points the metabolism increased following each type of treatment by the number of points by which it increased following the intravenous administration of 10 mg. of thyroxine and multiplying the result by 100. The figures for the second column have been calculated in a similar manner.

† For all the patients the increase in basal metabolism following the administration of desiccated thyroid has been changed to terms of 6.5 mg. of iodine by multiplying the number of points by which it increased by the fraction $\frac{2.83}{x}$ in which x = the dose of desiccated thyroid used. Excess calories have been changed in a similar manner.

‡ The effects of the various doses of thyroxine in this patient have been changed to terms of 10 mg. by multiplying the number of points the basal metabolism increased following their use by the fraction $\frac{10}{7.5}$.

same, but in the two patients (second and third) in whom the comparison was made, the effect of each was about from two to three times as great as that produced by the oral administration of the monosodium salt of thyroxine (from minus 31 to minus 23 per cent on the average).

There are some differences between the curves for desiccated thyroid and those for thyroxine. In the first four patients the maximum increase in basal metabolism appeared to occur proportionately more quickly following the oral administration of single large doses of desiccated thyroid (three days on the average) than following the intravenous administration of large doses of thyroxine (seven days on the average). In the first three patients the maximum increase also occurred more quickly following the oral administration of desiccated thyroid (three days on the average) than following the oral administration of thyroxine in alkaline solution (six days on the average). In patients 1 and 4 the maximum increase in metabolism was sustained for a shorter period following the oral administration of desiccated thyroid than following the intravenous administration of thyroxine, with the result that the total number of excess calories produced by desiccated thyroid was less than would be expected from the increase in basal metabolism. In the second and third patients, on the other hand, the number of excess calories produced by desiccated thyroid was roughly proportional to the increase in basal metabolism. In the first four patients the effect of desiccated thyroid was only 60 per cent as great, on the average, as that of thyroxine given intravenously, when the comparison was made on the basis of the number of excess calories produced, as compared with 76 per cent when the comparison was made on the basis of the increase in basal metabolism. This difference in the average effect was caused chiefly by the fact that in the first and fourth patients the effect of desiccated thyroid was only 62 and 50 per cent as great, respectively, as that of thyroxine given intravenously on the basis of excess calories, as compared with 97 and 84 per cent, respectively, on the basis of increase in the basal metabolism. The reason for this difference is unknown.

When the metabolism had shown its maximum change and had begun to decrease, the rate of change seemed to be similar for both desiccated thyroid and thyroxine. In the first four patients the average time represented by the descending portion of the curve for metabolism was forty-five days following the administration of large doses of desiccated thyroid, and forty-six days following the intravenous injection of thyroxine. In the first three patients the corresponding times for oral administration of desiccated thyroid, oral administration of thyroxine in alkaline solution and intravenous administration of thyroxine in alkaline solution were, respectively, forty, forty-four and forty-one days.

The higher the metabolism before treatment, the shorter is the duration of the effect, a phenomenon which appears to influence chiefly the number of excess calories produced rather than the absolute increase in the basal metabolism. Thus the increase in basal metabolism following the administration of 2.75 Gm. of desiccated thyroid (6.3 mg. of iodine) in the fifth patient was the same as that following the intravenous injection of 10 mg. of thyroxine (6.5 mg. of iodine) in the third patient, but a longer period was required for the basal metabolism to return to its level before treatment in the fifth patient because of its greater initial depression, and hence the number of excess calories was greater. Two observations which we have previously reported are pertinent to the interpretation of all data showing the calorigenic effect of thyroxine and of desiccated thyroid:

1. At levels of metabolism below the normal the effect of thyroxine given intravenously every day appears to be roughly proportional to the dose when the dose is not sufficient to raise the rate above the normal.[2]

2. A given dose of thyroxine has much less effect when the metabolism is normal before administration than when it is markedly reduced (minus 40 per cent).[5a]

Following every administration of single large doses of desiccated thyroid and of thyroxine the maximum clinical improvement was observed while the metabolism was falling, and in every instance the clinical condition of the patient was much better when the metabolism reached its premedication level than before any treatment was given.

It is of interest to combine the data of this paper with those previously reported in other parts of this study. This has been done in table 2. The comparisons made in this table seem to be justified because the initial depression of the basal metabolism was nearly the same for most types of treatment. It may be noted that, on the average, the increases in basal metabolism produced by the oral administration of monosodium thyroxine, thyroxine in alkaline solution and desiccated thyroid are, respectively, 22, 63 and 69 per cent as great as that produced by giving thyroxine intravenously in alkaline solution. In terms of excess calory production, the corresponding figures would be 18, 58 and 48 per cent, respectively. Thus, on the basis of equal iodine contents, the effect of oral administration of single large doses of desiccated thyroid is nearly the same, on the average, as that of oral administration of thyroxine in alkaline solution, while each produces from about two and one-half to three times as much effect as oral administration of monosodium thyroxine.

COMMENT

The reason for the variation in effect of a given dose of desiccated thyroid from patient to patient is not clear. Since most of the thyroid

TABLE 2.—*Summary of Effects of Single Large Doses of Desiccated Thyroid and of Thyroxine*

Medication*	Total Iodine Content of Substance Used, Mg.	Number of Patients	Number of Administrations	Average Basal Metabolic Rate Before Treatment, per Cent of Normal	Average Level to Which Basal Metabolic Rate Rose, per Cent of Normal	Average Change in Basal Metabolic Rate, Points	Average Number of Excess Calories Produced	Change in Terms of Average Response to Intravenous Injection of 10 Mg. of Thyroxine in Alkaline Solution	
								On Basis of Increase in Basal Metabolic Rate, per Cent†	On Basis of Excess Calories Produced, per Cent‡
10 mg.§ of pure synthetic thyroxine suspended in distilled water, by duodenum	6.5	3	3	—30	—29	1	.....	3	
10 mg.‖ of pure synthetic thyroxine suspended in distilled water, by mouth	6.5	4	4	—32	—30	2	.....	6	
10 mg.¶ of synthetic thyroxine in form of its monosodium salt (tablets), by mouth	6.5	6	6	—28	—21	7	.....	22	
Patients receiving monosodium salt by mouth, in whom excess calories were calculated	6.5	4	4	—30	—22	8	2,755	25	18
10 mg.# synthetic thyroxine in alkaline solution, by mouth	6.5	5	5	—31	—11	20	.....	63	
Patients receiving thyroxine in alkaline solution by mouth, in whom excess calories were calculated	6.5	4	4	—34	—12	22	9,010	69	58
2.83 Gm.** of desiccated thyroid (tablets), by mouth	6.5	5	5	—37	—15	22	7,405	69	48
10 mg.*** of thyroxine in alkaline solution, intravenously	6.5	6	8	—37	— 5	32	15,520	100	100

* The effect of a given dose of thyroxine was changed to terms of 10 mg. by multiplying the number of points the basal metabolism changed following its administration by the fraction $\frac{10}{x}$ in which x = the dose of thyroxine used. All thyroxine referred to in this table was the synthetic (Hoffmann-La Roche) except that so-called natural thyroxine (Squibb's) was used for four of the intravenous injections.

† The figures in this column were calculated by dividing the number of points by which the basal metabolism increased following treatment by 32 and multiplying the result by 100.

‡ The figures in this column were calculated by dividing the number of excess calories produced by each type of treatment by 15,520 and multiplying the result by 100.

§ The doses used were 10 mg., 40 mg. and 50 mg.

‖ The doses used were 10 mg., 30 mg., 40 mg. and 100 mg.

¶ The doses used were four of 10 mg. each, one of 30 mg. and one of 40 mg.

All the doses used were 10 mg. except one of 7.5 mg.

** For all the details of the administration of desiccated thyroid, see table 1.

*** All the doses were 10 mg., except two of 7.5 mg. Sodium hydroxide was used to dissolve the thyroxine for all administrations except one, in which potassium hydroxide was used (Mrs. C. F., table 1).

used was from one lot, the difference can scarcely be attributed to variation in potency, and some other explanation must be sought. The facts that the effect of thyroxine in alkaline solution is only 63 per cent as great on the average when given by mouth as when given intravenously and that desiccated thyroid has about the same effect, on the average, as thyroxine in alkaline solution when each is given by mouth suggest that some of the active principle of both is destroyed in the gastro-intestinal tract or fails to be absorbed. The data suggest that the process which is responsible for failure of absorption probably varies from patient to patient.

The variation in absorption which results in a variation from patient to patient in the ratio of the calorigenic action of desiccated thyroid by mouth from that of thyroxine given intravenously shows that comparisons of different preparations of desiccated thyroid with one another and with thyroxine in different patients may lead to erroneous conclusions and emphasizes the desirability of comparing the effects of different preparations in the same patient.

Since when small daily doses are given over a long period, the effects of desiccated thyroid by mouth and of thyroxine intravenously appear to be the same on the basis of equivalent iodine contents, it is possible that absorption is more efficient when desiccated thyroid is given in small daily doses than when it is administered in single large doses.

SUMMARY

In five patients with myxedema the oral administration of single doses of desiccated thyroid caused an increase in basal metabolism of from minus 37 to minus 15 per cent on the average, and the production of 7,405 excess calories on the average for every 6.5 mg. of iodine.

In four patients in whom the comparison was made, the calorigenic effect of the oral administration of a single large dose of desiccated thyroid varied from 59 to 97 per cent (average, 76 per cent) of the effect of intravenous administration of a single large dose of thyroxine containing the same amount of iodine when the comparison was made on the basis of the increase in basal metabolism, and from 50 to 69 per cent (average 60 per cent) when the comparison was made on the basis of the number of excess calories produced.

In three patients in whom the comparison was made, the increases in basal metabolism produced by these large doses of desiccated thyroid were from 75 to 133 per cent as great as those produced by the oral administration of thyroxine in alkaline solution on the basis of equal iodine contents, and on the average the effects of the two were approximately the same.

If the data of the present study are combined with those previously reported, it is found that on the average the increases in basal metabolism produced by the oral administration of monosodium thyroxine, thyroxine in alkaline solution and desiccated thyroid are, respectively, 22, 63 and 69 per cent as great as that produced by the intravenous injection of thyroxine. If the comparison is made on the basis of excess calories produced, the corresponding figures are, respectively, 18, 58 and 48 per cent.

MYASTHENIA GRAVIS ASSOCIATED WITH THYMOMA

REPORT OF TWO CASES WITH AUTOPSY

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Since Weigert [1] first described the presence of a thymoma in a case of myasthenia gravis, reports of this association have become increasingly frequent, and great interest has been aroused in its significance. We have been fortunate in observing two patients with myasthenia gravis in whom thymomas were found at necropsy. Alter and Osnato [2] suggested "that all cases of myasthenia gravis with definite pathologic observations should be recorded, not only for the reason of their rarity, but that they may serve toward the construction of an explanation of the pathology of the disease, confirm part of it or offer useful hints for future observation." For these reasons the following cases are reported.

REPORT OF CASES

CASE 1—*History.*—K. F., a Greek housewife, aged 27, was admitted to the Lenox Hill Hospital from the ophthalmologic dispensary on Dec. 19, 1932, complaining of drooping of both eyelids. Three weeks before admission, she had suffered from a mild attack of influenza. At that time she also had a transient weakness of the left arm. Shortly thereafter, she noticed a drooping of the left upper eyelid, which was followed in rapid succession by involvement of the right eyelid and complete inability to move either eyeball. She occasionally "saw double."

Her history was essentially unimportant except for an attack of acute articular rheumatism ten years before, which had lasted for one month. Her menses were normal. She was married and had three children. One daughter, aged 2 years, was deaf and dumb.

Physical Examination.—Physical examination revealed an obese white woman who was not acutely ill. The pulse rate was 88; the temperature, 99.8 F.; the respiratory rate, 20, and the blood pressure, 120 systolic and 80 diastolic. Her face had a masklike expression. Partial ptosis of both eyelids, complete bilateral

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From the medical service of Dr. A. L. Garbat and the Achelis Laboratory of the Lenox Hill Hospital.

1. Weigert, C.: Pathologisch-anatomischer Beitrag zur Erbischen Krankheit, Neurol. Centralbl. **20**:594, 1901.

2. Alter, N. M., and Osnato, M.: Myasthenia Gravis with Status Lymphaticus and Multiple Thymic Granulomas, Tr. Am. Neurol. A. **55**:303, 1929.

external ophthalmoplegia and paralysis of convergence were present. The pupils were equal and slightly irregular, and reacted sluggishly to light and distance. The fundi and visual fields were normal. There was a marked fetor ex oris, and many teeth were missing. The tonsils were enlarged and cryptic, and contained cheesy material. The heart, lungs and abdomen were normal. The reflexes were active and equal, and no pathologic reflexes were elicited. The sensorium was intact.

Laboratory Data.—Examination of the blood revealed: red cells, 5,000,000; hemoglobin (Sahli), 85 per cent; white cells, 8,250; neutrophils, 79 per cent, and lymphocytes, 21 per cent. Blood chemistry showed: urea nitrogen, 10.8 mg. per hundred cubic centimeters; creatinine, 0.5 mg.; uric acid, 2.8 mg.; sugar, 74 mg.; carbon dioxide-combining power, 55.7 volumes per cent; serum calcium, 10.6 mg. per hundred centimeters, and serum phosphorus, 3.7 mg. The Wassermann reaction of the blood was negative. The cerebrospinal fluid, obtained by lumbar puncture, was clear and under normal pressure; it contained 2 leukocytes and 1 red blood cell per cubic millimeter and 57 mg. of sugar per hundred cubic centimeters: the globulin, Wassermann and colloidal gold tests were negative. Routine urinalysis gave negative results except for the presence of calcium oxalate crystals. Determination of the total creatinine excreted in a twenty-four hour specimen of urine revealed 0.54 Gm. A sugar tolerance test (100 Gm. of dextrose orally) gave the following results:

	Blood Sugar Mg. per 100 cc.	Urine Sugar Mg. per 100 cc.
Fasting	94	Neg.
45 min. after dextrose	266	0.3
2 hrs. after dextrose	270	1.0

Roentgenograms of the skull and chest showed no abnormality. On stimulating the biceps and peroneus muscles with faradic current, the strength of response showed a progressive diminution in marked contrast with that of normal controls of the same age group.

Course.—The initial diagnosis was postinfluenzal epidemic encephalitis. The patient was treated symptomatically with a preparation of potassium iodide, sodium salicylate, strychnine and caffeine. By the early part of February, a change in the clinical picture was evident. General asthenia was progressive and extreme. The patient complained of dizziness, generalized body pains and headaches. Not only was she completely bedridden, but she was unable to lift her head from her pillow. There was such marked fatigue of the jaws on chewing and dysphagia that it became necessary to feed her through a duodenal tube. There was almost no masseter or temporal muscle action, and she tired quickly on talking. Though normal at first, her speech would take on a mumbling and lisping character after a few minutes. A slight right facial weakness was noted (fig. 1).

On Feb. 14, 1933, she was seen by Dr. Foster Kennedy, who made the diagnosis of myasthenia gravis on the basis of the bizarre clinical picture. She was given ⅜ grain (0.375 Gm.) of ephedrine sulphate twice daily, which resulted in a slight improvement in her condition. She looked brighter and began to move her upper eyelids slightly.

On March 5, the patient suddenly collapsed. Marked inspiratory distress was present. The respirations were chiefly abdominal, and the nostrils were dilated. She became cyanotic; the palpebral fissures were widened, the pupils were dilated and did not react to light, and no pulse was felt at the wrists. On stimulation with epinephrine, caffeine and metrazol, and with oxygen furnished through a nasal

catheter, she rallied and in several hours was no longer dyspneic or cyanotic. The pulse rate was 112 and regular. That day the temperature, which throughout the whole course of the illness had been normal, rose to 100.6 F.

The next morning the patient appeared brighter and oxygen was temporarily discontinued. Her pulse rate was not very forceful, but it was regular. The heart sounds were of fair quality. The blood pressure was 120 systolic and 85 diastolic. The lungs were clear, except for occasional crepitant râles at both bases.

On March 7, two days after her initial collapse, dyspnea and cyanosis suddenly recurred, and she complained of a choking sensation. She sank rapidly and, in spite of artificial respiration and stimulation by epinephrine and caffeine, died.

Necropsy.—Macroscopic Examination: The body was that of an obese white woman, 150 cm. in length. The pupils were equal and slightly irregular, and were in mid-dilatation. Livor and rigor mortis were marked.

The skull was not examined. The pleural cavities contained no free fluid. The right lung lay free in the pleural cavity and weighed 325 Gm. The pleural surface was smooth and glistening, except for extensive purplish-red, slightly depressed

Fig. 1 (case 1).—Photograph showing the masklike facies, ptosis of the eyelids, and right facial weakness.

areas over the lower lobe. On section, the lung was edematous and reddish brown. The portions of the lung beneath the depressed areas were beefy red and airless. The left lung was firmly adherent to the chest wall at its apex and weighed 250 Gm. It was similar to the right lung in appearance and on section.

The pericardial sac contained no excess fluid. The heart was small, weighing 225 Gm. The surface was smooth and glistening. There was a moderate amount of epicardial fat. On section, the myocardium was reddish brown. The valves, aorta and coronary arteries showed no gross abnormalities.

In the anterior mediastinum was a mass, apparently composed of two structures, extending down the anterior surface of the pericardium. The upper half had the appearance of a hyperplastic thymus gland, except that it was somewhat firmer than normal; the lower half, rising from the inferior pole of the gland, was a firm, oval, encapsulated nodular mass, measuring approximately 4 cm. in its longest and 2.5 cm. in its shortest diameter. On section, it was grayish white and trabecular and contained several small areas of calcification.

The thyroid and parathyroid glands were grossly normal.

The anterior abdominal wall measured 5.5 cm. in thickness, only 0.5 cm. of which was muscle. The muscle fibers were dull brown. The diaphragm was

extremely thin and almost translucent. The peritoneal cavity contained no excess fluid. The liver weighed 1,600 Gm. Its capsule was smooth and not thickened. On section, it was congested and reddish brown. The gallbladder and bile ducts appeared to be normal.

The spleen weighed 200 Gm. The capsule was smooth and not thickened, and the surface was dark red. On section, the pulp was soft and congested. Malpighian corpuscles were visible.

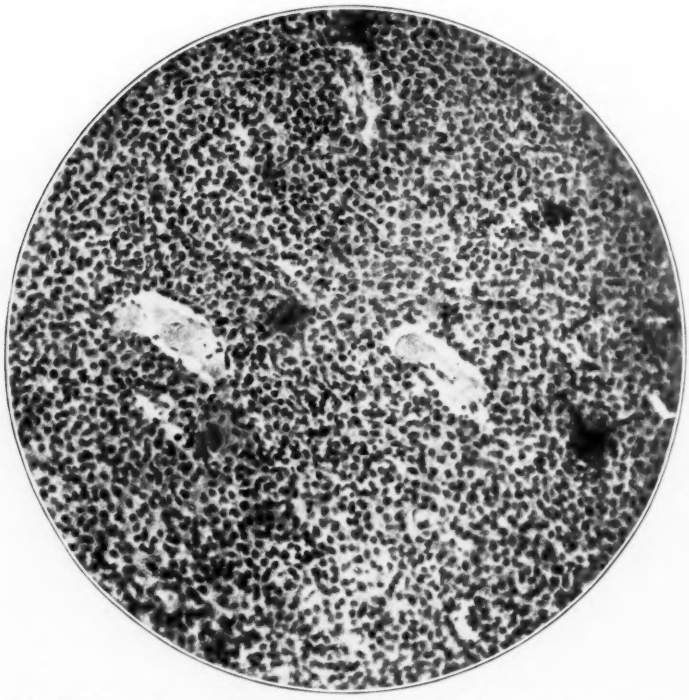

Fig. 2.—Photomicrograph of a section of thymoma, showing the anastomosing sheets of polyhedral cells and the scanty lymphocytes. Hematoxylin and eosin stain; × 200.

The left kidney weighed 125 Gm. The capsule was smooth and was stripped with ease. The surface was reddish brown, streaked with yellow opaque areas. On section, it had the same mottled appearance and was deeply congested. The cortex was of normal thickness and the cortical markings were distinct. The right kidney weighed 150 Gm. and was similar in appearance to the left.

The other viscera exhibited no gross abnormalities.

Anatomic Diagnosis: There were: congestion, edema and atelectasis of the lungs; atrophy of the heart; hyperplasia of the thymus gland; thymoma; atrophy of the skeletal muscles, and congestion of the liver, spleen and kidneys.

Microscopic Examination: Sections through the upper portion of the mediastinal mass showed it to be the thymus gland. The lower circumscribed mass had the typical structure of a thymoma. It was completely encapsulated by a thick layer of dense hyaline fibrous tissue which contained occasional small focal collections of round cells. The blood vessels in the capsule exhibited moderate irregular knoblike hyperplasia of the intima. Sections from different portions of the tumor showed a somewhat varied picture. For the most part, it was composed

Fig. 3.—Photomicrograph of the same portion of tumor as shown in figure 2 under high power magnification. Hematoxylin and eosin stain; × 850.

of large, anastomotic sheets of polyhedral cells, separated by small amounts of vascular fibrous tissue. (fig. 2). These cells had large vesicular nuclei and definite nucleoli. The cytoplasm was acidophilic and granular, and the cell outlines were indistinct. Some of the cells had a flattened appearance (fig. 3). Small round cells were scanty and were situated mainly about the blood vessels. In other areas, large amounts of dense, fibrous stroma divided the tumor cells into irregular islands, and round cells were more conspicuous. In still other areas, the structure approached that of the thymus gland, round cells predominating over the thin cords of polyphedral cells (fig. 4). The latter lay adjacent to the capillaries.

Mitoses were infrequent. No plasma cells, eosinophils, giant cells or Hassall's corpuscles were seen.

Marked edema, congestion and large areas of atelectasis were noted in the lungs.

A deposit of anthracotic pigment, edema and slight endothelial hyperplasia were present in a bronchial lymph node.

The muscle fibers of the heart were thin and atrophic, and many showed an increased amount of pigment about the nuclei. The striations were indistinct,

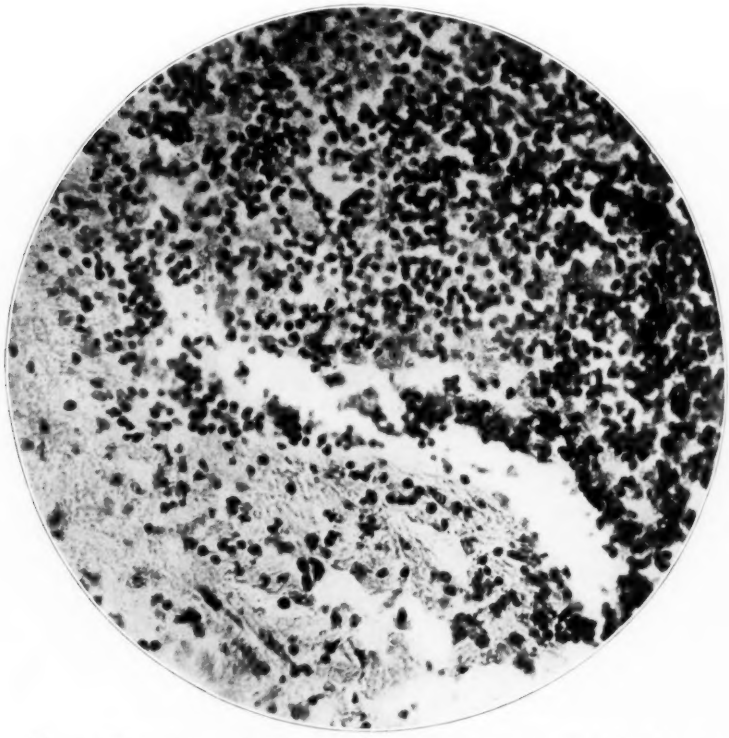

Fig. 4.—Photomicrograph of a section of the same tumor, showing the resemblance of areas to the thymus gland. Hematoxylin and eosin stain; × 200.

and diffuse hyaline degeneration was present. Occasionally a muscle fiber was necrotic, and in these areas there were localized collections of round cells (fig. 5). The stroma was slightly increased and was edematous.

The liver cells were small and atrophic, and were the seat of an advanced fatty degeneration. In areas, the cell outlines were indistinct, and early necrosis was visible. The sinuses were diffusely and widely dilated. Kupffer cells were prominent, and some of them contained cellular detritus.

In the spleen the fibrous trabeculae were somewhat thickened. The veins, especially those within the trabeculae, were greatly congested. The reticulum

was moderately thickened in areas. The sinuses contained an increased number of polymorphonuclear leukocytes, and the endothelium was hyperplastic. The pulp was irregularly edematous and showed scattered neutrophils and small amounts of hemosiderin pigment, both free and within the large mononuclear cells. The arterioles exhibited rather advanced hyalinization of their walls and narrowing of their lumens. The malpighian corpuscles contained an occasional secondary nodule.

Fig. 5.—Photomicrograph of a section of cardiac muscle, showing a lymphorrhage about a necrotic fiber. Hematoxylin and eosin stain; × 400.

In the kidneys intense congestion and small hemorrhages were present, especially in the medulla, where many of the collecting tubules were filled with blood. Degeneration of the tubular epithelium was slight. In the suprarenal glands the cortical cells exhibited marked vacuolar degeneration which involved practically all the cells, but was most marked in the inner layers. Many of the cells of the zona reticularis were completely necrotic and had disappeared, giving these areas a glandlike appearance. Many of the remaining cells were deeply pigmented. There were intense congestion and many small hemorrhages, especially in the zona reticularis. The medulla was normal except for edema.

The pancreas appeared to be normal except for autolysis. There was no evidence of abnormality in the uterus or ovaries, except a few small hemorrhages and edema of the endometrium. The thyroid showed a slight increase in the colloid, with flattening of the acinose cells. The parathyroids appeared to be normal. Examination of striated muscle from the abdominal wall and diaphragm showed the fibers to be atrophic. The nuclei were often arranged along the periphery of the fibers, and occasional small collections of round cells (lymphorrhages) were present between them.

Fig. 6.—Photomicrograph of a section of thymoma, showing the lobulation of the tumor by dense bands of fibrous tissue. Hematoxylin and eosin stain; ×200.

Case 2.—*History.*—L. K., a Lithuanian, aged 54 years, was admitted to the Gouverneur Hospital on Dec. 9, 1932, complaining of extreme weakness. For the past year he had been under treatment at the allergy clinic for frequent attacks of asthma. About one month before admission, he became extremely weak and was unable to talk consecutively for any length of time without his voice becoming inaudible. He had a heavy feeling in his head and also a feeling of warmth at times. About three weeks before admission he "lost his appetite for sleep," so that for several days he had not slept, day or night. There had been a moderate loss of weight in the past month.

Physical Examination.—The temperature was 99.6 F.; respiratory rate 20; the pulse rate 80, and the blood pressure, 192 systolic and 108 diastolic. The face was expressionless, and a slight ptosis of both upper eyelids was present. The pupils were equal and regular, and reacted to light and in accommodation. The fundi were normal. No ocular palsy was demonstrated. Conjunctival anesthesia and corneal hypesthesia were present. The apex beat of the heart was in the sixth interspace within the midclavicular line. The sounds at the apex were booming in quality. No murmurs were audible. The respiratory excursions were small, with prolonged expiratory murmur. Occasional sibilant and sonorous râles were heard over both lungs. Examination of the abdomen gave negative results. The abdominal and radioperiosteal reflexes were absent. The knee jerk reflexes were elicited by reenforcement. There were no pathologic reflexes or sensory disturbances. Coordination was good, and there was no ataxia.

A lumbar puncture revealed clear fluid which contained but 1 cell per cubic millimeter. The globulin test gave negative results. Six drops of the spinal fluid reddened Benedict's solution. Reactions to the Wassermann and Kahn tests were negative. The colloidal gold curve was 0001122322.

A few hours after admission, the patient died suddenly.

Necropsy.—Macroscopic Examination: The body was that of a well developed and well nourished white middle-aged man, 154 cm. in length. The pupils were equal and regular and were in mid-dilatation. Rigor mortis was absent. The brain and its coverings were apparently normal. The right lung was densely adherent at the apex and weighed 380 Gm. The left lung lay free in the pleural cavity and weighed 300 Gm. There was an old scar at the right apex, and a moderate emphysema of the anterior borders of each upper lobe was seen.

The region of the thymus was occupied by a very dense, encapsulated, sausage-shaped mass, measuring 9 by 3 cm. It lay transversely across the trachea, great vessels and upper attachments of the pericardium. It was difficult to cut, and its surface presented a lobulated structure. The lobules were creamy yellow, and were separated by dense bands of fibrous tissue.

The pericardial sac contained no excess fluid. The heart weighed 300 Gm., and its surface was smooth and glistening. The left ventricle was moderately hypertrophied. The aorta and the left coronary artery exhibited a few atheromatous plaques. The valves were grossly normal. The myocardium was light brown.

The liver weighed 1,530 Gm. Its capsule was not thickened, and the cut surface was reddish brown. The gallbladder and bile ducts showed no gross abnormalities.

The spleen weighed 150 Gm., and on section the pulp was congested and soft.

The kidneys weighed 130 Gm. each. The capsules were stripped with some difficulty and revealed a fine granular surface. On section, the cortices were slightly narrowed and the markings blurred. The blood vessels were prominent.

The other viscera exhibited no gross abnormalities.

Anatomic Diagnosis: There were chronic adhesive pleuritis; pulmonary emphysema; hypertrophy of the left ventricle, atherosclerosis of the aorta and left coronary artery; thymoma; congestion of the liver and spleen and arteriosclerotic nephritis.

Microscopic Examination: Sections through the mediastinal tumor showed it to be completely encapsulated by a thick layer of dense fibrous tissue from which wide trabeculae radiated into its substance, giving it a lobulated appearance. The trabeculae had a peculiar arrangement, branching off the main trunk like the limbs of a tree. The parenchyma was composed of large polyhedral or flattened reticular cells (fig. 6). Lymphocytes were scanty, and only an occasional plasma cell was present.

The brain, lungs, liver and spleen were normal, except for congestion. The heart showed hypertrophy of muscle fibers, moderate degeneration and small focal collections of round cells.

The kidneys exhibited an advanced arteriolosclerosis, with many glomeruli in various stages of replacement by fibrous tissue. Slight degenerative changes were present in the tubular epithelium.

The suprarenal capsule was somewhat thickened. The cortical cells showed a marked vacuolar degeneration, especially in the zona fasciculata. In some areas the degeneration had progressed to actual necrosis of the cells. Marked hyperemia, numerous small hemorrhages and large collections of hemosiderin pigment were present, especially in the zona reticularis.

COMMENT

A perusal of the literature reveals that the diagnosis of myasthenia gravis frequently offers great difficulties. Because visual symptoms are usually the first to appear, an ophthalmologist is consulted before an internist. The initial diagnosis is frequently encephalitis. Both of our cases were so diagnosed. The difficulty in differentiating between the two conditions is further enhanced by the fact that cases of epidemic encephalitis simulating myasthenia gravis have been reported.[3] However, if the possibility of myasthenia gravis is borne in mind, the simultaneous occurrence of a large number of incongruous changes soon makes the diagnosis of encephalitis untenable. As in case 1, the absence of fever and disturbance of sleep, the normal spinal fluid, the bizarre clinical picture of normal reflexes and sensorium, associated with muscular weakness, and the quick fatigue on chewing and talking, with recovery after rest, lead to the recognition of the malady. In addition, various laboratory procedures have been advocated as diagnostic aids.

A number of workers (Pierchalla,[4] Mella,[5] Reuter,[6] and Keschner and Strauss[7]) reported a shadow in the region of the thymus shown by roentgen rays in cases of myasthenia gravis. Based on the frequent association of a thymoma in this disease, such a finding would support the diagnosis. However, the absence of a shadow is of no significance, as many cases without this tumor have been described; also, when it actually is present, a roentgenogram of the chest can fail to reveal it. This point was well demonstrated in case 1.

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3. Grossman, M.: Epidemic Encephalitis Simulating Myasthenia Gravis, J. Nerv. & Ment. Dis. **55**:32, 1922.

4. Pierchalla, L.: Ueber die Röntgenbehandlung der hyperplastischen Thymus bei Myasthenia pseudoparalytica, Therap. Halbmonatsh. **16**:504, 1921.

5. Mella, H.: Irradiation of the Thymus in Myasthenia Gravis, M. Clin. North America **7**:939, 1923.

6. Reuter, A.: Zur Kenntnis der Myasthenia gravis, Deutsche Ztschr. f. Nervenh. **120**:131, 1931.

7. Keschner, M., and Strauss, I.: Myasthenia Gravis, Arch. Neurol. & Psychiat. **7**:337 (March) 1927.

The so-called myasthenic or Jolly reaction, first described by Jolly [8] in 1895, makes possible a more accurate determination of the fatigability of the skeletal muscles, and is of service in the early or mild cases.

Williams and Dyke,[9] Hart [10] and Nielsen and Roth [11] observed a diminished sugar tolerance in myasthenia gravis. The test performed in case 1 gave a typical diabetic curve.

A diminished urinary excretion of creatinine in myasthenia was reported by Williams and Dyke [9] and by Monrad-Krohn and Forsberg.[12] According to Peters and Van Slyke,[13] the level of total creatinine excretion in twenty-four hours in a normal person is constant and is dependent on his size and muscular development. It may be expressed in the form of a creatinine coefficient: $\frac{\text{mg. total creatinine in 24 hour specimen of urine}}{\text{body weight, Kg.}}$. Normally, the coefficient, based on total creatinine, ranges between 14 and 22 in women. It was 8.4 in case 1.

According to Noyes,[14] lymphorrhages can be demonstrated in the skeletal muscles in about 86 per cent of the cases of myasthenia gravis. In obscure cases, a biopsy of the skeletal muscle may be advisable.

There are two other diseases, syphilis of the central nervous system and tumor of the brain, which must be considered in the differential diagnosis. The former can be excluded by the negative reaction of the blood and spinal fluid to the Wassermann test and the normal gold curve, and the latter by the absence of localizing signs, the normal spinal fluid and roentgenograms of the skull.

The prognosis in this disease must always be guarded. Sudden death in the form of respiratory failure has been frequently reported but not sufficiently stressed.

The outstanding pathologic changes in myasthenia gravis are the abnormalities of the thymus and the so-called lymphorrhages of the skeletal muscles.

The association of abnormalities of the thymus with myasthenia gravis is more than an accidental finding. Starr, quoted by Bell,[15] in

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8. Jolly, F.: Ueber Myasthenia gravis pseudoparalytica, Berl. klin. Wchnschr. **32**:1, 1895.

9. Williams, B. W., and Dyke, S. C.: Observations on Creatinuria and Glycosuria in Myasthenia Gravis, Quart. J. Med. **15**:269, 1921.

10. Hart, H. H.: Myasthenia Gravis with Ophthalmoplegia and Constitutional Anomalies in Sisters, Arch. Neurol. & Psychiat. **18**:439 (Sept.) 1927.

11. Nielsen, J. M., and Roth, P.: Myasthenia Gravis: Report of Three Cases, J. Nerv. & Ment. Dis. **67**:32, 1928.

12. Monrad-Krohn, G. H., and Forsberg, R.: Contribution to the Pathology of Myasthenia, Acta psychiat. et neurol. **5**:247, 1930.

13. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932.

14. Noyes, A. P.: A Case of Myasthenia Gravis with Certain Unusual Features, Rhode Island M. J., **13**:52, 1930.

reviewing two hundred and fifty autopsies of myasthenia gravis, noted that a pathologic condition of the thymus was recorded in 28 per cent of the cases. Bell [15] collected reports of all cases with autopsy from 1901, when Weigert [1] first described a thymic tumor in association with myasthenia gravis, to 1917. He found that the thymus was definitely abnormal in 49 per cent of the cases. Of the 49 per cent, hyperplasia was noted in 30 per cent, and thymoma in 19 per cent of the cases. Since 1917, no large group of cases which came to autopsy has been reported. The literature contains a considerable number of case reports, but most of them are of cases which did not come to autopsy. It is thus difficult to state the exact proportions of thymic tumors in myasthenia gravis with any degree of accuracy. It is conceivable that they are present in a greater percentage of cases than Bell's figures indicate.

Moreover, it is frequently difficult to determine when the thymic hyperplasia has assumed the characteristics of a thymoma. As in our two cases, the tumor is usually of moderate size, is definitely encapsulated and exhibits no metastases, unless the lymphorrhages in the muscles are considered as such. On section, it is cream or lemon yellow in color and often shows dense fibrous trabeculations. Microscopically, the parenchyma is composed of lymphocytes, plasma cells and large polyhedral cells. The last-mentioned cells resemble, and are supposedly derived from, the reticular cell. Occasionally, giant cells and Hassall's corpuscles are found. The structure varies with the number of polyhedral cells present, and different areas of the same tumor are frequently dissimilar in this respect. When polyhedral cells are numerous, the lymphocytes are scanty or absent and the structure resembles a lymphosarcoma. When scanty, the structure is that of a simple hyperplasia. Occasionally, as in case 2, a characteristic lobulation is found.

The significance of thymic hyperplasia and thymomas in myasthenia gravis is still shrouded in mystery, but that some relationship does exist is shown not only by the frequency of their occurrence but by the good results reported in this disease following extirpation and irradiation of the thymus. In this connection, it is of interest that status lymphaticus resembles myasthenia gravis in the asthenia and liability to sudden death. However, the fact that abnormalities of the thymus have not been found in all cases of myasthenia gravis strongly militates against the assumption of an etiologic significance.

A possible explanation for the thymic abnormalities may lie in the suprarenal changes. In our two cases, the cortical cells were the seat of an extensive vacuolar degeneration which in areas had gone on to complete necrosis of the cells. A number of authors called attention to

15. Bell, E. T.: Tumors of the Thymus in Myasthenia Gravis, J. Nerv. & Ment. Dis. **45**:103, 1917.

the suprarenals in this disease. Mandelbaum and Celler[16] described acute congestion and a large lymphorrhage in the suprarenal cortex. Marie, Bouttier and Bertrand[17] found an atrophy of the suprarenal glands as a factor in the disease. Alter and Osnato[2] noted that the chromaffin substance of the suprarenals was diminished and that the medulla was atrophic.

The relationship between lesions of the suprarenal cortices and asthenia, such as occurs in Addison's disease and in chronic suprarenal insufficiency, needs no elaboration here, but that many such cases exhibit a hyperplasia of the thymus at autopsy is not so well known.[18] Following suprarenalectomy in the rabbit and rat, and less frequently in the dog and cat, there occurs a rapid and remarkable regeneration of the thymus, even in old animals.[19] In infants, beginning about the second week of extra-uterine life, there occurs a spontaneous involution of the suprarenal cortex, coincident with a rapid increase in the size of the thymus.[20] Finally, Marine assembled much evidence in support of the contention that status lymphaticus in man is dependent, in part at least, on a deficiency of some internal secretion common to both the suprarenal cortex and the gonads.[21] All these observations speak for a reciprocal relationship between the thymus and the suprarenal glands and strongly support the hypothesis that the pathologic changes in the thymus are secondary to a degenerative lesion of the suprarenal glands. The cortical extract which has been found to be efficacious in Addison's disease may not be the only hormone secreted, and in analogy to the pituitary syndromes, a derangement of another hormone of the suprarenal gland may be the causative factor in myasthenia gravis.

In each of the cases cited, lymphorrhages similar to those in skeletal muscles were found in the cardiac musculature. This is an infrequent observation. In addition to these lymphorrhages, the cardiac muscu-

16. Mandelbaum, F. S., and Celler, H. L.: A Contribution to the Pathology of Myasthenia Gravis: Report of a Case with Unusual Form of Thymic Tumor, J. Exper. Med. **10**:308, 1908.

17. Marie, P.; Bouttier, H., and Bertrand, I.: Etude anatomo-clinique d'un cas grave de myasthénie de Erb-Goldflam, Ann. de méd. **10**:173, 1921.

18. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

19. Marine, D.; Manley, O. T., and Baumann, E. J.: The Influence of Thyroidectomy, Gonadectomy, Suprarenalectomy and Splenectomy on the Thymus Glands of Rabbits, J. Exper. Med. **40**:429, 1924. Jaffe, H. L.: The Influence of the Suprarenal Gland on the Thymus: Regeneration of the Thymus Following Double Suprarenalectomy, ibid. **40**:325, 1924. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on Suprarenal Glands in Reference to Functions of Their Internal Portions, Bull. Johns Hopkins Hosp. **25**:287, 1914.

20. Thomas, E.: Zur Histologie der Säuglingsnebennieren, Deutsche med. Wchnschr. **37**:236, 1911.

21. Marine, D.: Status Lymphaticus, Arch. Path. **5**:661 (April) 1928.

lature showed degenerative changes. The cause of these lymphorrhages is obscure, an infectious or toxic agent usually having been hypothecated. Whatever the cause, findings in our cases indicate that the heart muscle is not spared.

Atrophy of the skeletal muscle, such as occurred in case 1, is also an infrequent observation.

The therapy of myasthenia gravis has been empirical, and therefore varied. Schumacher and Roth [22] reported the case of a patient with myasthenia gravis associated with hyperthyroidism who benefited greatly by thymectomy. This is a radical procedure, and there is not a sufficient number of patients so treated to warrant its acceptance.

Good results by means of irradiation of the thymus were obtained by various workers.[23] Mella stated, "The myasthenic syndrome may follow on tumor of the thymus and disappear on irradiation of the thymus region." Moreover, Pierchalla [4] advocated this form of treatment as a therapeutic test, even though thymic enlargement may not be demonstrable by roentgenograms.

To combat symptoms of suprarenal insufficiency, the extract of its cortex was employed by Marie and his co-workers [17] with some success. Edgeworth [24] tried five differently prepared suprarenal substances and found that the beneficial effects were not constant, nor was muscle power improved.

Large doses of strychnine were used for this disease by Dana [25] with good results. Edgeworth was the first to point out the beneficial results derived from ephedrine. It will be recalled that the patient in case 1 showed definite clinical improvement with the use of this drug.

Remen [26] and Boothby [27] recently reported excellent results following the use of glycocoll. Glycocoll presumably acts in some way on the metabolism of the muscle cell. Since Wolff, Keutmann and Cobb [28]

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22. Schumacher and Roth: Thymektomie bei einem Falle von Morbus Basedowi mit Myasthenie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:746, 1913.

23. Pierchalla.[4] Mella.[5] Keschner and Strauss.[7]

24. Edgeworth, Harriet: A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, J. A. M. A. **94**:1136 (April 12) 1930.

25. Dana, C. L.: Myasthenia Gravis: A Therapeutic and Clinical Study, J. A. M. A. **78**:261 (Jan. 28) 1922.

26. Remen, L.: Zur Behandlung der Myasthenia pseudoparalytica mit Glykokoll, Deutsche med. Wchnschr. **58**:889, 1932.

27. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:557 (Sept. 28) 1932. Boothby, W. M.; Adams, M.; Power, M. H.; Edgeworth, H.; Moersch, F. P.; Woltman, H. N., and Wilder, R. M.: Myasthenia Gravis: Second Report on the Effect of Treatment with Glycine, ibid. **7**:737 (Dec. 28) 1932.

28. Wolff, H. G.; Keutmann, H., and Cobb, S.: The Electromyogram in Myasthenia Gravis, Brain **51**:508, 1928.

showed that the fundamental defect in myasthenia gravis is peripheral to the ventral horn cells and probably in the muscle cell, such therapy is rational.

SUMMARY

1. The clinical course and findings at autopsy in two cases of myasthenia gravis associated with thymomas are reported.

2. Some diagnostic features of myasthenia gravis are presented: the shadow in the region of the thymus noted in roentgenograms; the diminished creatinine output in a twenty-four hour specimen of urine; the decreased sugar tolerance; the Jolly reaction, and the presence of lymphorrhages in skeletal muscle obtained through biopsy.

3. The frequent association of thymomas with the myasthenic syndrome is again emphasized.

4. Because of the degenerative changes found in the suprarenal cortices in our cases and in others in the literature, and because of the reciprocal relationship which apparently exists between the suprarenal cortex and the thymus, a new theory is propounded to explain the occurrence of thymomas in this disease.

5. The cardiac musculature in our two cases exhibited the typical lymphorrhages which have usually been described as being present only in the skeletal muscles.

6. Atrophy of the skeletal muscles, noted in one of our cases, is an infrequent observation.

7. A summary of the treatment of myasthenia gravis recorded in the literature is presented.

NEUROGENIC EROSIONS AND PERFORATIONS OF THE STOMACH AND ESOPHAGUS IN CEREBRAL LESIONS

REPORT OF SIX CASES

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In 1859, von Rokitansky [1] described two forms of softening of the stomach, one a gelatinous softening said to occur in infants and a second form occurring both in children and in adults. The description in each case suggests that the processes are similar. In describing the former he said:

> It appears to be a metamorphosis—a softening—of the mucous membrane of the fundus, which extends to the muscular coat and the peritoneum converting them and the intervening interstitial cellular tissue into a grayish or grayish-red transparent jelly with a yellowish tinge, through which single dark brown streaks, the broken down blood vessels, are observed to pass. . . . The softened portion of the stomach tears at the slightest touch; it dissolves between the fingers, and perhaps in rare cases these rents occur during life, but probably oftener after death, giving rise to effusion of the gastric contents into the abdominal cavity. The process is not, however, limited to the stomach, but frequently extends to the neighboring tissues, and chiefly to the muscular organs, and especially to the diaphragm. Here, too, perforation is the final result, and with it there is effusion of the gastric contents into the left pleura.

Continuing, he said of gelatinous softening: "It is frequently founded upon a demonstrable affection of the brain, principally hypertrophy or hydrocephalus." Rokitansky described his second form of softening as "distinguished [from gelatinous softening] by an absence of colour in the softened tissues, or rather by their colour. The parietes of the stomach are converted into a more or less saturated dark brown, or blackish pulp." Discussing the etiology, he said: "It occurs both in children and adults as a sequela of acute affections of the brain and its membranes, and more especially of tubercular meningitis at the base of the brain."

Read before the Chicago Neurological Society, Nov. 16, 1933.

From the Departments of Neuropsychiatry and Pathology, the University of Wisconsin.

1. von Rokitansky, C. F.: Pathological Anatomy, London, The Sydenham Society, 1859, p. 35.

It remained for Cushing,[2] in his Balfour lecture, to define a clinical syndrome in which gastromalacia and ulcers of the upper portion of the gastro-intestinal tract were definitely related to disease of the interbrain. Eleven cases, illustrative of several types of lesions associated mainly with cerebral neoplasms, form the basis of his monograph. The ground had been prepared for Cushing by observations and experimental data pointing the way to this association. Cushing's theory of parasympathetic stimulation resulting in ulcer and softening has been fortified by observations made by him on human subjects into whom intraventricular injections of pharmacodynamic drugs were made.

The purpose of this article is to present a series of cases in support of Cushing's hypothesis of association with disease of the interbrain.

REPORT OF CASES

CASE 1.—*Abscess of the frontal lobe with terminal meningitis; gastromalacia with perforation through the diaphragm.*

G. J., a woman, aged 48, was admitted to the medical service[3] on Jan. 26, 1933, appearing very ill and mentally confused. She had an infected lesion of the left cheek, which was treated by radium in February 1932, and in May 1932 she had a thyroidectomy and soon thereafter an operation on the sinus. There followed a gradual change in personality, with lethargy and despondency alternating with marked restlessness and mild mania at times, together with weakness and loss of weight.

Examination revealed emaciation, pale, dry, scaling skin, exophthalmos on the left, a left naris full of pus, two large, discrete nodules in the left posterior cervical lymph chain, changes in the base of each lung, fever and cardiac hyperactivity. A blood count revealed 4,090,000 erythocytes; 9,100 leukocytes (86 per cent neutrophils) and hemoglobin 60 per cent.

At the neurologic examination (on February 9, after she had been in a comatose state for hours) the essential observations were: edema of the disks, proptosis of the left eyeball with edema and induration of the tissues about the eyeball and firmness of the globe; flushing of the left cheek; stiff neck; weakness of all the extremities, exaggerated reflexes, bilateral Babinski reflexes, and muscular twitchings. During the examination, serous fluid flowed freely from the left nostril. Two hours later, foul pus was draining from this nostril. The temperature (axillary) was 100.4 F., the pulse rate, 112, and the respiratory rate, 36. The previous two weeks had been marked by rises in temperature to 102.6 F., the temperature at times dropping to normal and some days not rising higher than 100 F. The leukocyte count was 19,300, with 92 per cent neutrophils.

A diagnosis of abscess of the left frontal lobe and meningitis was made. A spinal puncture yielded clear fluid under increased pressure, with 70 cells and a colloidal gold curve of 00123333210. Four hours later the temperature, pulse

2. Cushing, Harvey: Peptic Ulcer and the Interbrain, in Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 175.

3. Dr. Marie Carns permitted us to use this clinical material.

rate and respiratory rate suddenly increased to 102.6 F., 140 and 44, respectively, and the blood pressure was 156 systolic and 60 diastolic. From then on the temperature (axillary) mounted to 107 F. before death at 4 a. m.

Autopsy, five hours after death, revealed a dilated left pupil with bulging of the left globe. Beneath the dura of the left frontal lobe an abscess was found extending from 1.5 cm. posterior to the tip of the frontal lobe to the anteroposterior portion of the left thalamus, its walls thick and covered with greenish, ragged, necrotic material. The base of the brain was covered with a thick green purulent material, and pus from a perforation of the abscess was extravasated into the sella turcica, the cribriform plate and the orbit.

Histologic examination of the interbrain (lenticular nucleus) revealed congestion, hemorrhage, areas of necrosis and perivascular lymphoid cell infiltration, with phagocytosis of hemosiderin (fig. 1). A section from the base of the brain showed

Fig. 1 (case 1).—A section from a focus in the interbrain at the periphery of the abscess; × 125.

acute purulent meningitis. There was an acute inflammatory process in the pituitary gland.

The abdomen contained about 300 cc. of coffee-ground fluid. The stomach was dilated and the wall was extremely thin, with a perforation 6 by 2 cm. near the fundus on the anterior surface. The edges of the perforation were dark green, soft and thin, with a minimal acute reaction. The diaphragm in the region of the cardiac end of the stomach was digested, with a perforation 2 by 2 cm. into the thorax. Examination of the left side of the thorax revealed 250 cc. of fluid similar to that found in the abdomen, with digestion of the parietal, visceral and diaphragmatic pleural surfaces. The left lung was completely atelectatic at the base, with emphysema of the upper lobe and marked emphysema of the entire right lung.

Histologic examination of the stomach revealed a partial loss of mucosa in all sections taken near the areas of perforation and a complete loss of mucosa with plasma cell and lymphoid cell infiltration around the area of perforation. Exami-

nation of the left lung revealed, in addition to the digestion of pleurae and atelectasis, early patchy areas of bronchopneumonia.

CASE 2.—*Acute encephalitis, with marked disturbance of the vegetative nervous system; multiple erosions of the stomach and perforation of the esophagus.*

W. B., a man, aged 28, was brought in in a semicomatose state on March 7, 1933. For four weeks he had complained of having a cold, but no one observed that he was ill until a few days before the onset of the acute condition, when he complained of headache and body pains and seemed to be less active and very drowsy. On March 6 he was found asleep, and when aroused he continued to complain of headache and body pain.

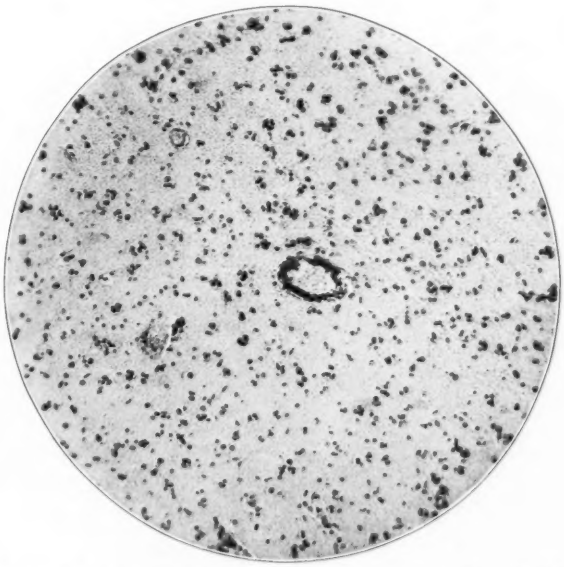

Fig. 2 (case 2).—A section from the midbrain (in a case of encephalitis), showing dilated blood vessels and perivascular infiltration; × 50.

The patient could be aroused, but made only monosyllabic responses. During the first hour in the hospital his temperature was 101 F., the pulse rate 112, and the respiratory rate, 24. The blood sugar was 160 mg. per hundred cubic centimeters, and the nonprotein nitrogen, 37 mg. Physical examination revealed a stiff retracted neck and back; there was no Kernig sign, but the patient's legs resisted manipulation. The blood pressure was 156 systolic and 100 diastolic, and the reflexes were normal. A lumbar puncture yielded clear spinal fluid under normal pressure, with 5 cells and a colloidal gold curve of 0012221000. The spinal fluid sugar was 86 mg. per hundred cubic centimeters. The blood sugar at the same time was 113 mg. It will be noted that in an hour's time the sugar quotient dropped 47 mg. without any fluid having been added to the circulation. A blood count taken at the same time was as follows: erythrocytes, 6,370,000; hemoglobin, 90 per cent; white cells, 11,900; polymorphonuclears, 95 per cent. From this point

Fig. 3 (case 2).—The stomach and esophagus, showing gastromalacia and perforation of the esophagus.

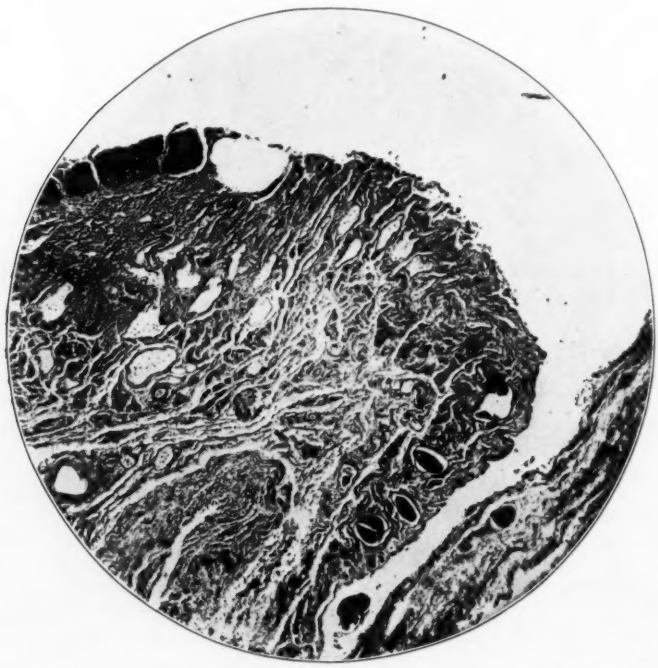

Fig. 4 (case 2).—A section from the edge of the perforation of the esophagus (fig. 2); × 30.

his temperature mounted steadily, reaching 106.4 F. (axillary) on March 8. He perspired profusely at intervals. On March 8, the following observations were made: deep coma; color, livid; reactive, miotic pupils; a Kernig sign on the left; general hyporeflexia and blood pressure, 109 systolic and 70 diastolic. On March 9 a blood count revealed: 7,240,000 erythrocytes, hemoglobin 100 per cent, and 26,900 leukocytes. The patient died at 5:15 a. m. on March 10. The temperature at 4 a. m. was 106.4 F. The pulse could not be counted with accuracy after midnight. The respiratory rate varied from 20 to 32 until 11:15 p. m. on March 9, when it rose to 40.

Thus, in this case the entire symptomatology—hyperpyrexia, sweating, plethoric appearance, polycythemia, hypersomnia and disturbances of the pulse rate, respiration and blood pressure—suggests the disease process to be centered in the hypothalamic region.

Autopsy, four hours later, revealed congestion of the cerebral vessels. Microscopic examination of the cortex and the midbrain revealed widely dilated vessels with perivascular lymphocytic infiltration and slight degeneration of the ganglion cells (fig. 2). In the left pleural cavity was 500 cc. of coffee-ground fluid; after removal of the fluid it was found that the visceral, posterior parietal and diaphragmatic structures as well as the pleura over the vertebrae had been partially digested, leaving the lung with a granular hemorrhagic surface and exposing the mediastinal structures. A perforation in the esophagus (fig. 3) about 3 cm. in length was found on the left posterolateral surface just above the diaphragm; the edges of the perforation were extremely thin, soft and stained dark green. The wall of the stomach was also very thin, especially in the cardiac portion, where there were multiple erosions of the mucosa.

Histologic examination of the esophagus (fig. 4) revealed congestion and edema, with widely dilated vessels, lymphocytic and plasma cell infiltration and a complete loss of mucosa near the area of perforation with a small amount of hemorrhage in the submucosa. The stomach was extremely atrophic, there being only a few remaining undifferentiated glands with much congestion, lymphocytic infiltration and edema.

CASE 3.—*Tumor of the posterior fossa, sexual precocity, gastromalacia; perforation of the stomach and diaphragm; localized peritonitis and acute pleurisy.*

L. N., a boy, aged 10, was brought to the hospital by his parents on April 18, 1933. His illness started one year before, with frontal headaches, but did not seem serious until six weeks previous to admission to the hospital. At that time he complained of double vision, the eyes appeared to protrude and the left eyeball turned inward. Two weeks later the Wassermann reaction of the blood was 2+, then 3+, while the reactions of the blood of the parents were negative. During the three weeks just previous to hospitalization, his vision became impaired, and he staggered and held his head to the left. He became restless and irritable and had difficulty in expressing himself. During the twenty-four hours before admission he had polyuria, photophobia and two convulsions.

Physical examination revealed a boy of precocious physical and sexual development. He measured 60 inches (152.4 cm.) and weighed 85 pounds (38.6 Kg.) as against 51 inches (129.5 cm.) and 61 pounds (27.7 Kg.), the normal for his age. There were fixed pupils, bilateral weakness of the sixth nerve, inability to roll the eyes upward or downward, choked disks (6 diopters), hypotonicity, increased tendon reflexes, abortive ankle clonus, a bilateral Babinski sign, resistance to flexion of the neck, generalized hyperesthesia, marked ataxia and dysmetria. The pulse rate was rapid, the temperature, normal, and the blood pressure, 124 systolic

and 94 diastolic. The Wassermann reaction of the blood was 4+. Because of the positive Wassermann reaction a cisternal puncture was made, which revealed bloody fluid under increased pressure. During the last week of life he was stuporous, with normal temperature, pulse rate and respiration until eleven hours

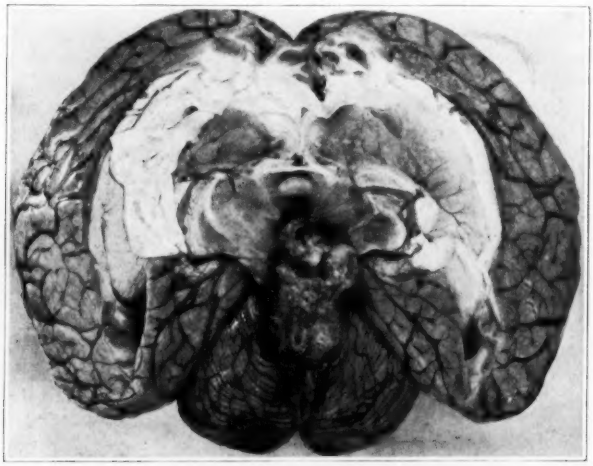

Fig. 5 (case 3).—The brain, showing the tumor extending into the third ventricle.

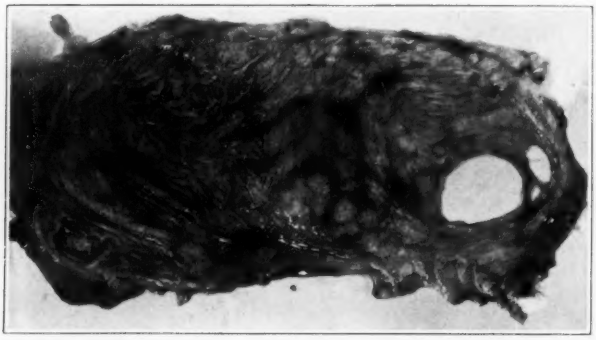

Fig. 6 (case 3).—The stomach showing areas of erosion, hemorrhage and perforations.

before death, when they suddenly changed—the pulse and respiratory rates increasing rapidly until death with hyperthermia (temperature, 105 F., axillary).

Autopsy, twenty-eight hours after death, revealed a large tumor arising from the superior surface of the cerebellum, measuring 7 by 3.5 by 3 cm. and extending forward into a dilated third ventricle, the medial surface of the thalami showing impressions of the tumor (fig. 5), which proved to be a teratoma. In the cardiac

portion of the stomach (fig. 6) were two perforations on the greater curvature, 3 by 1.5 cm. The surrounding wall of the stomach was thin and showed small areas of hemorrhage. The neighboring peritoneum, including the surfaces of the spleen and liver, was roughened by a granular exudate. The diaphragm above the involved portion of the stomach proved to be the location of a perforation of the diaphragm, 3 cm. in diameter, irregular in shape with softened, discolored margins. The left pleural cavity contained 500 cc. of dark brown fluid. The parietal and visceral pleura showed granular acute pleurisy and erosion.

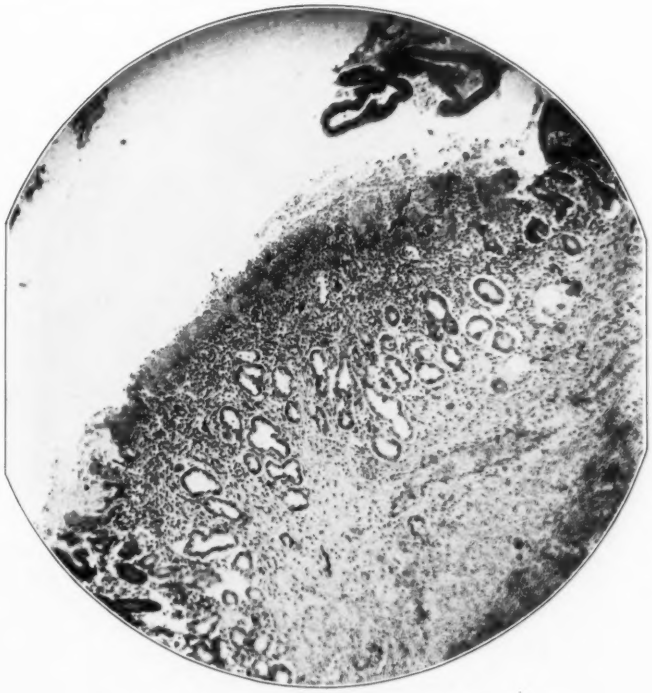

Fig. 7 (case 4).—A section from the pylorus; × 30.

Microscopic examination of the stomach lesion revealed inflammatory edema with diffuse submucosal hemorrhage and infiltration by lymphocytic and plasma cells.

The interest resulting from the occurrence of these three cases caused Dr. Bunting to recall the circumstance of an infant dying of hemorrhage at birth and presenting changes in the pyloric mucosa.

Case 4.—A girl, after a difficult labor, was delivered by forceps. Twitching of the extremities and spasticity of the legs led to a cisternal puncture which yielded bloody fluid. The infant died fourteen hours after birth with hyperthemia (105.8 F.).

Autopsy, five hours post mortem, revealed edema with subcutaneous hemorrhage throughout the posterior portion of the scalp and several localized small subcutaneous hemorrhages in the anterior portion. The cranial cavity contained bloody fluid, both above and below the tentorium cerebelli, and there was generalized congestion of the pia-arachnoid. The anterior tip of the left temporal lobe appeared somewhat softer than the rest of the brain.

Microscopic examination of the brain revealed extreme congestion. Histologic study of a section of the stomach taken for routine examination revealed superficial antemortem necrosis of the pyloric mucosa with leukocytic infiltration (fig. 7).

CASE 5.—*Tumor of the corpus callosum; antemortem hemorrhage; gastromalacia.*

F. J., a man, aged 31, had been known to have a brain tumor since April 26, 1932. He had symptoms of about one year's duration, beginning with headaches,

Fig. 8 (case 5).—The brain, showing extensive invasion by the tumor of the ventricles and neighboring structures.

followed by jacksonian convulsions, periods of dysphasia, right facial weakness, progressive right spastic hemiplegia, choking of the optic disks (6 diopters), dysarthria and a defect of memory. A craniotomy failed to reveal the tumor in the expected location. This was followed by two courses of roentgen therapy. He was admitted to the hospital for the third time on Sept. 17, 1933. A summary of the observations on that occasion follows: marked mental changes, partial motor aphasia, astereognosis, right facial weakness, apraxia of the tongue, right homonymous hemianopsia, right hemiplegia (arm more involved than the leg) and choked disks (5 diopters). A ventriculogram was made through a posterior trephination opening, revealing a midline lesion which obliterated the midportion of the lateral ventricles, flattening and depressing the roof of the third ventricle. The course of events was marked by increasing mental deterioration and stupor and a constantly elevated blood pressure, but a normal pulse rate, until the last week. During the last week he became generally rigid and took no food but was given from 600 to 1,500 cc. of fluid daily. A large emesis of bright blood occurred on

November 15, and on one occasion subsequently there was an emesis of dark, thick, yellowish material. Fever (temperature not higher than 102.6 F.) and an increase in the pulse rate from 130 to 180 and in the respiratory rate from 30 to 60 marked the last two days. Death occurred on November 22.

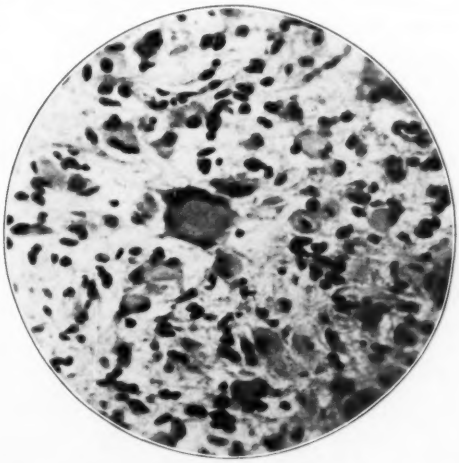

Fig. 9 (case 5).—A section from the tumor shown in figure 8; × 280.

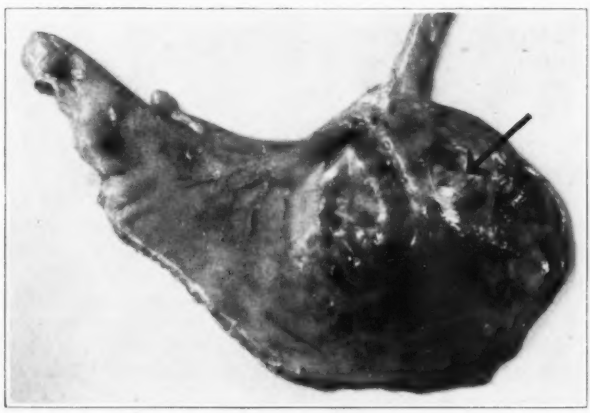

Fig. 10 (case 5).—The stomach, showing gelatinous softening with hemorrhage and perforation (arrow).

Autopsy, thirteen hours after death, revealed an extensive brain tumor which occupied the middle fossa, extending from the inferior surface of the frontal lobes posteriorly 8 cm. to involve the left internal capsule and laterally through the body of the corpus callosum into each hemisphere (invading the lateral ventricles),

measuring 9 cm. in its widest portion. Microscopic examination of the thalamus (fig. 9) revealed a spongioblastoma multiforme.

The stomach (figs. 10 and 11) was dilated and contained 300 cc. of greenish-black liquid which showed 2 degrees of free acid and 100 degrees of total acid. The cardia of the stomach was extremely thin, there remaining only a delicate transparent membrane. The thinning involved the proximal third of the stomach. A rupture 2.5 cm. in diameter had occurred in the cardia anteriorly, from which a small amount of bile-stained liquid had escaped. There was a slight degree of peritoneal reaction in the vicinity of the rupture. A fairly sharp line across the fundus differentiated the very thin proximal portion from the distal thicker portion. However, the distal two thirds of the wall of the stomach was thinner than normal.

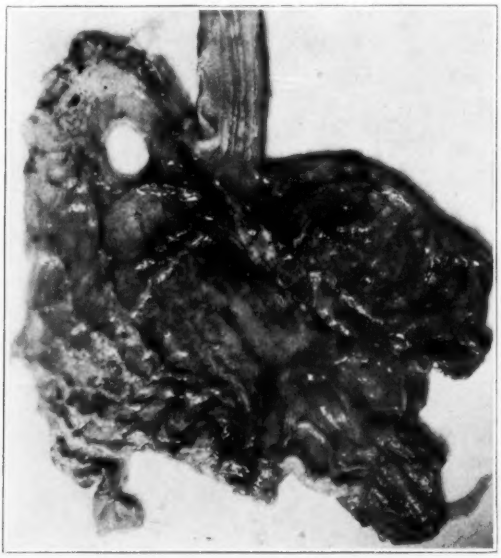

Fig. 11 (case 5).—The stomach (fig. 9) opened, showing perforation and hemorrhage.

Histologic examination near the rupture revealed amorphous material which contained only a few strands of muscle fiber. Other sections from the surrounding gelatinous area revealed an extreme lymphocytic infiltration and dilated blood vessels. Sections from the distal two thirds showed a similar but less intense process.

CASE 6.[4]—*Hypertensive cardiovascular disease with hemorrhage into the basal ganglions; gastromalacia; esophagomalacia and rupture.*

H. S. E., a traveling salesman, aged 46, on January 31 was found unconscious in his car, parked at the side of a highway. He was taken to a hospital in a

4. Dr. S. B. Pessin, pathologist, St. Mary's Hospital, Madison, gave the details of this case. The pathologic specimens were presented before the staff of the Wisconsin General Hospital.

town nearby, where he died four days later without regaining consciousness. The only findings reported were fever, slow pulse rate and bloody spinal fluid. Two months before, his physician had found retinal hemorrhages and a blood pressure of 260 systolic and 130 diastolic, and had advised him not to drive an automobile.

The autopsy revealed an extensive hemorrhage involving the thalamus, the lentiform nucleus and the internal capsule, which had ruptured into the right lateral ventricle. The cerebral vessels showed much atherosclerosis, particularly those of the circle of Willis. The mucosa of the stomach was hyperemic, and there were two perforations, one 3.5 by 2.5 cm. on the anterior surface 5 cm. below the cardiac sphincter and one 3.5 cm. in diameter on the posterior wall which included 1 cm. of the esophagus. The left side of the thorax contained 1,000 cc. of thin bloody fluid, while a smaller amount was found immediately below the diaphragm on the left side. There were associated hemorrhagic pleuritis of the left lung with partial atelectasis of the lower lobe, emphysema of the right lung, localized peritonitis and perisplenitis. The observations confirming the clinical diagnosis of hypertensive (malignant) cardiovasculorenal disease will be omitted.

COMMENT

Each of the patients was comatose for twenty-four hours or longer before death and could not have felt the pain of rupture. No patient was actively digesting food during the twenty-four hours preceding death. In none was there distention of the abdomen. In the first three cases a sudden increase in the pulse rate and respiratory rate developed several hours before death, which seems to mark the occurrence of the perforation and effusion of gastric contents into the peritoneal or pleural cavity. In case 5, there was a gastric hemorrhage a week before death.

There seems to be no question as to the antemortem nature of these observations. In all the cases histologic examination of the gastrointestinal structures showed hemorrhage and infiltration by plasma cells and leukocytes, definitely indicating active circulation and response of the tissues. The acute pleurisy and localized peritonitis in case 3 and the atelectasis and secondary emphysema and early bronchopneumonia in case 1 are indubitable evidence that the effusion of gastric contents into the left side of the thorax and abdominal cavity occurred some hours before death. If the sudden increase in the pulse rate and respiratory rate is accepted as marking the moment of rupture, in case 1 it took place twelve hours before death; in case 2, six hours before, and in case 3, eight hours before, death. In case 5 a hemorrhage occurred a week before death. Large quantities of coffee-ground material, in the absence of active digestion at the time of death, and the combined acid of 100 degrees in the contents of the stomach post mortem in case 5 are evidence that there was active secretion in the stomach.

Cushing's hypothesis of a parasympathetic center in the diencephalon has received support from Beattie,[5] working at McGill University.

5. Beattie, J.: Relation of the Tuber Cinereum to Gastric and Cardiac Functions, Canad. M. A. J. **26**:278, 1932.

This investigator exposed the third ventricle and stimulated the lateral margin of the infundibulum of his animal with an electrode. Through the open abdomen various observations were made on the viscera. The stomach showed increased peristalsis and secretion of acid. There developed increased tonus and peristaltic waves in the bladder. Hyperemic patches appeared in the mucous membrane of the lesser curvature after one-half hour of stimulation. Section of the vagus abolished these effects. Further proof that the vagus supplies the end-organ in the stomach with stimulation from the tuberal centers was derived by suturing the central end of the cut vagus with the peripheral end of a severed phrenic nerve. After waiting one hundred and eighty days for regeneration, stimulation of the tuber cinereum caused contraction of the diaphragm. Electrocardiograms made during the stimulation experiments elicited prolonged auriculoventricular conduction time.

Little [6] and his colleagues, working in Cushing's laboratory, injected pilocarpine hydrochloride into the lateral ventricles and found that gastric ulcers developed in 94 per cent of their rabbits. Microscopic examination of these gastric lesions revealed areas of local anemia in the mucosa accompanied by surface hemorrhage and liquefaction necrosis extending as far as the muscularis.

Cushing [7] demonstrated the effect of the intraventricular injection of solution of pituitary as well as of pilocarpine hydrochloride in man. Reactions to the two preparations were similar, although solution of pituitary did not produce vomiting. The injection of 2.5 mg. of pilocarpine hydrochloride resulted in a rise in blood pressure, flushing, borborygmi, nausea, vomiting, profuse diaphoresis, a drop in temperature and, finally, blood-streaked vomitus. The duration of symptoms was three hours.

The interbrain is the higher center not only for the parasympathetic system but for the sympathetic system, as shown by Beattie,[5] who, by stimulating the posterior hypothalamus, produced secretion of epinephrine, an increase in the heart rate and diminished auriculoventricular conduction time.

It is with more than passing interest that these theories have been viewed, for experience with encephalography has led to the conviction that the immediate and sometimes the more remote effects of this procedure are due to stimulation of the centers about the third ventricle, brought about by distention. Vomiting and retching are an almost con-

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6. Little, R. A.; Bishop, C. C., and Kendall, L. G.: The Production of Gastric Lesions in Rabbits by Injection of Pilocarpine into the Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. **45**:227, 1932.

7. Cushing,[2] p. 67.

stant feature during the replacement of spinal fluid by air and occur first when from 40 to 70 cc. of spinal fluid has been withdrawn (from 30 to 60 cc. of air replacing the fluid). This occurs at intervals throughout the procedure. Profuse perspiration and pallor are the rule. The pulse rate frequently slows to between 40 and 50 toward the end of or shortly after the procedure. The blood pressure often shows a drop, but may show an unusual rise later, after the patient has returned to bed. Blood-streaked vomitus has occurred on several occasions, and abdominal pain and desire to urinate have been noted.

In one patient, A. F., with an unconfirmed neoplasm of the middle fossa, the effects of encephalography were not evident until eight hours later, when, with the patient in marked distress, the house physician found the upper part of the abdomen distended. On inserting a stomach tube, 1,000 cc. of thick, tarry material was removed, which took on the appearance of coffee-grounds toward the end of the aspiration. No evidence of further hemorrhage appeared and gastric studies a month later showed no defect in the mucosa. These effects occur in spite of the administration of 9 grains (583.2 mg.) of phenobarbital sodium, which depresses the hypothalamic area, according to Cushing.[8] It has been observed that vomiting does not occur unless the ventricles are evacuated, and that in cases of marked internal hydrocephalus few or no symptoms develop. The lateral ventricles are apparently emptied before vomiting occurs, judging from the amount of fluid which has been removed, leading to the belief that it is the emptying of the third ventricle and the distention by air which results in the disturbances in the vegetative system.

SUMMARY

Six cases of brain lesions associated with erosions and perforations of the upper part of the gastro-intestinal tract are reported.

Experimental evidence of the location of parasympathetic and sympathetic centers in the interbrain is introduced.

The effect of encephalography on these centers in the interbrain is discussed.

NOTE.—Since this paper was submitted for publication two more cases have come to our attention.

H. K., a man, aged 46, had meningitis secondary to an abscess of the orbit which occurred in a degenerating tumor (adamantinoma of the left maxilla and orbit which had received roentgen therapy). When first seen his temperature was 105 F. He died in the hospital, on Sept. 19, 1934, four days after the onset, with

8. Cushing,[2] p. 219.

a temperature of 107 F. His stomach contained a large quantity of greenish-black fluid which reacted positively to the benzidine test for blood and contained 50 degrees of total acid. The mucosa of the lesser curvature was studded with numerous petechial hemorrhages. Microscopic examination of this area revealed mucosal congestion, hemorrhages and submucosal edema. The interbrain was not studied. The surface of the left hemisphere was covered with a purulent exudate.

D. T., a girl, aged 12, had symptoms of disease of the basal ganglions for four years previous to admission to the hospital on June 20, 1934. She died in a tonic convulsion on September 20, with a temperature of 105 F. During the last two hours she vomited coffee ground material which reacted positively to the benzidine test for blood. Postmortem examination was limited to the brain, in which an infiltrating neoplasm was located in the basal ganglions and upper part of the brain stem which proved to be a spongioblastoma. The gastric contents which were aspirated yielded a large quantity of material similar to that vomited before death.

ADAMS-STOKES SYNDROME WITH TRANSIENT COMPLETE HEART BLOCK OF VAGOVAGAL REFLEX ORIGIN

MECHANISM AND TREATMENT

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AND
EUGENE B. FERRIS JR., M.D.
BOSTON

Complete auriculoventricular dissociation has been studied extensively by physiologists and clinicians. Through its unique physiologic mechanisms, the development of heart block often is associated with striking clinical manifestations. The dissociation of the cardiac chambers also permits an insight into otherwise concealed functions of the human heart. The observations to be reported here have yielded information which throws light on the mechanism and treatment of a rare type of heart block heretofore not completely understood.

REPORT OF A CASE

CASE 1.—*History.*—On July 14, 1933, F. H., a white man, aged 64, was admitted to the hospital in a stuporous state, following attempted suicide with illuminating gas. The cause of this act was despondency because of fainting spells believed to be incurable, from which he had suffered for ten years. The attacks manifested themselves in sudden dizziness or fainting lasting a minute or two and were usually precipitated by swallowing food, particularly sticky food, such as peanut butter and crackers. Sometimes only a sip of water caused an attack. The attacks developed at any time during the day, but most frequently in the morning after the first bit of food or drink was taken. The dizziness and fainting were associated with pains along the lower portion of the sternum, descending toward the stomach. At first the attacks appeared only two or three times a month; later, however they occurred two or three times daily.

The patient visited the outpatient department of the Boston City Hospital in 1926. The physical examination at that time showed no abnormality. Roentgen examination of the esophagus, however, revealed a dilatation of the lower portion, with a small diverticulum at the level of the fourth costochondral junction (fig. 1). Several unsuccessful attempts were made to reproduce the attacks by swallowing. Tincture of belladonna was given in adequate doses, which decreased the number of the attacks.

When admitted to the hospital, the patient was slightly cyanotic; the face was flushed, and the respirations were slow and deep. These signs disappeared within

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and Department of Medicine, Harvard Medical School.

twenty-four hours after recovery from the gas poisoning. The head and the shape and expansion of the thorax were normal. The cardiac dulness was 10 cm. to the left of the midsternal line in the fifth costal interspace, 8 cm. in the fourth and 5 cm. in the third. The heart sounds were regular but rather distant. The aortic second sound was louder than the pulmonary second sound. A faint systolic murmur was heard over the apex. The cardiac rate was usually slow—48 per minute. The peripheral vessels were moderately thickened and tortuous. The pulses were equal. The arterial pressure fluctuated between 94 and 140 mm. of mercury systolic and between 56 and 80 mm. diastolic; the venous pressure was less than 6 cm. of water. The rest of the physical examination revealed no abnormality except a slightly enlarged liver.

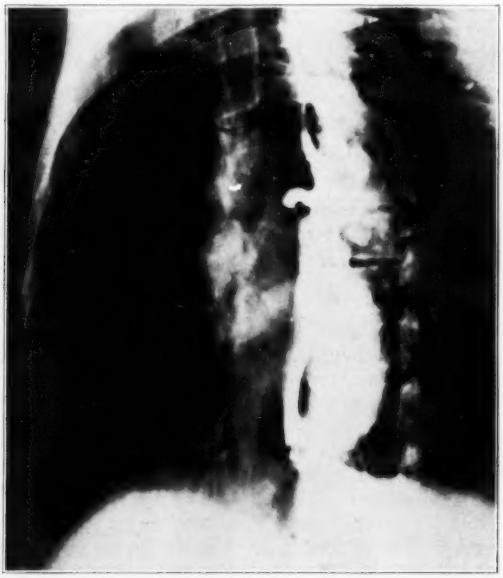

Fig. 1 (case 1).—Roentgenogram of the esophagus filled with barium solution. Appearance of the diverticulum in the left oblique anterior position. The wide, rounded white area below the diverticulum is the cardiac shadow.

The red blood cell count was 4,600,000 per cubic millimeter, with a hemoglobin of 81 per cent. The white cells were normal in number and in type. The blood sugar during fasting was 94 mg., and the nonprotein nitrogen 25 mg. per hundred cubic centimeters. Examination of the urine revealed no abnormalities.

The Cardiovascular System Between Attacks.—As indicated, except for moderate thickening of the peripheral blood vessels, the cardiovascular system revealed no organic lesions. The patient was active and quick in locomotion without experiencing dyspnea. Repeated electrocardiograms failed to reveal any abnormality (fig. 2). Sinus bradycardia was present at times. There was also a prolongation of the P R interval up to 0.21 second on some occasions. The heart rate at rest varied from 48 to 66 per minute. The arterial blood pressure also showed variation at rest.

Spontaneous Attacks.—On three occasions we had an opportunity to study the patient during attacks. Following the swallowing of food, he complained of pain over the lower third of the sternum. His face became pale, and his voice somewhat hoarse. The heart rate became slower and irregular. The venous pulsations over the neck were more rapid than the apical heart rate. The patient became listless, and in a sitting position his head drooped forward. In one or two minutes he regained consciousness, which was associated with flushing of the face and the return of normal cardiac rhythm. We had no opportunity during the spontaneous attack to obtain an electrocardiogram.

Roentgen and Fluoroscopic Observations.—Repeated roentgen studies revealed that the lower portion of the esophagus was dilated, and that at the lower third there was a hook-shaped diverticulum pointing anteriorly (fig. 1). The cardiac shadow and pulsations were normal. The pulmonary fields were clear except for a few small shadows interpreted as calcifications. The lesion of the esophagus was considered a traction diverticulum, resulting from previously active tuberculosis of a lymph node.

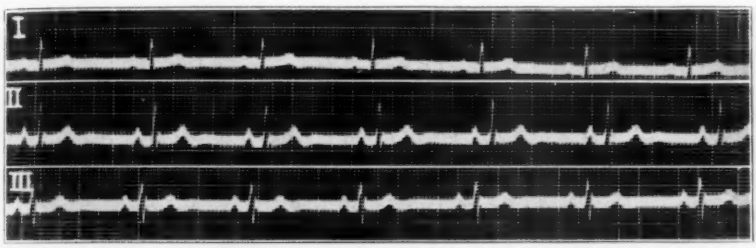

Fig. 2 (case 1).—The normal electrocardiogram, leads I, II and III. The P R interval was from 0.19 to 0.2 second.

Induction of Attacks.—Following the discovery of the diverticulum of the esophagus, the question was raised as to the possible relationship between the mechanical irritation of the diverticulum and the fainting spells. In order to test the relationship, a small rubber balloon, connected with a duodenal tube and with a mercury manometer, was swallowed by the patient. Under the fluoroscope it was placed at a level corresponding to the diverticulum of the esophagus and was then distended. A pressure of from 100 to 120 mm. of mercury regularly induced a sensation of distress behind the sternum, followed by dizziness, blurring of vision and temporary loss of consciousness. Release of the pressure promptly relieved the symptoms. The patient stated repeatedly that all of the manifestations associated with the induced attacks corresponded to those experienced during the spontaneous attacks.

Electrocardiograms obtained during such an observation revealed a complete auriculoventricular dissociation (figs. 3, 4 and 5). Depending on the speed with which the pressure within the balloon rose, the onset of the heart block was instantaneous or delayed by a few beats. Coincidentally with the slowing of the heart rate there occurred a moderate fall in the blood pressure which varied from 28 to 40 mm. Control observations by distention above and below the level of the diverticulum failed to induce symptoms or heart block.

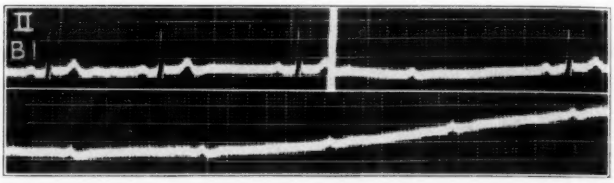

Fig. 3 (case 1).—Electrocardiogram, lead II. Continuous tracing representing control electrocardiogram and the instantaneous onset of heart block with ventricular standstill following inflation of the balloon (the vertical white line). An Adams-Stokes attack occurred.

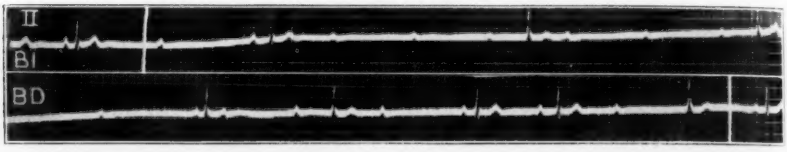

Fig. 4 (case 1).—Electrocardiogram, lead II. Continuous tracing representing the onset and disappearance of complete heart block with irregular ventricular rhythm. The vertical white line in the control tracing (*BI*) indicates elevation of pressure in the balloon, and the vertical white line in the lower tracing (*BD*) indicates deflation of the balloon, followed by the return of sinus rhythm. During the period of block two types of ventricular complexes were present. An Adams-Stokes attack occurred.

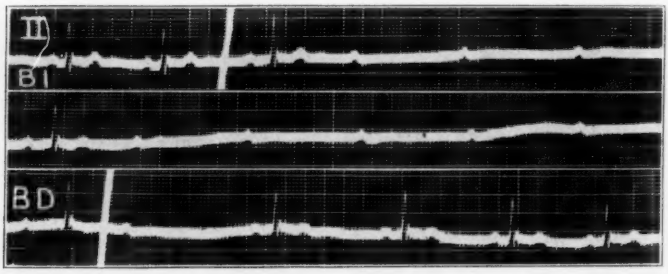

Fig. 5 (case 1).—Electrocardiogram, lead II. Continuous tracing representing the effect of inflation (vertical white line of *BI*) and of deflation (vertical white line of *BD*) of the balloon. Following inflation of the balloon, heart block with a long period of ventricular standstill developed. An Adams-Stokes attack occurred.

The Effect of Drugs.—The fact that the Adams-Stokes attacks and heart block could be induced with regularity by means of identical stimuli afforded an opportunity for comparing the effects of therapeutic measures used in the treatment of the Adams-Stokes syndrome occurring with the onset of heart block.

Barium chloride was administered orally at regular intervals over a period of forty-eight hours in doses of 30 mg., with a final dose of 60 mg. During the period of administration the patient suffered from four spontaneous attacks. Following this period, after 300 mg. had been administered, the experiments with the balloon were performed. Severe Adams-Stokes attacks followed as usual. The administration of barium chloride was therefore continued in doses of 30 mg. A total of 150 mg. was administered within the next eighteen hours, during which period the patient suffered from an additional attack. Two balloon experiments performed at the end of this period resulted in the usual symptoms and electrocardiographic findings, as shown in figure 6. The patient later took 30 mg. four times a day for a period of seventeen days, and, according to his report, suffered from nine spontaneous attacks of varying severity. He believed, however, that he was somewhat improved.

Epinephrine was used in a 1:1,000 solution. One dose of 0.5 mg., administered subcutaneously, induced no appreciable change in the cardiac rate or in the

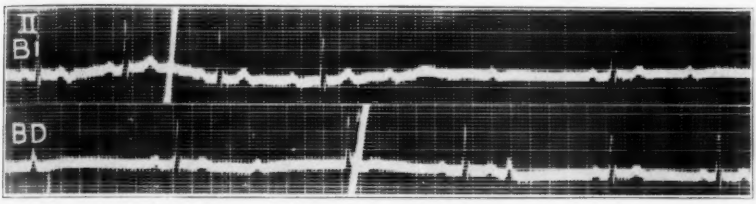

Fig. 6 (case 1).—Electrocardiogram, lead II. Continuous tracing representing the lack of beneficial effect of barium chloride. Following gentle inflation of the balloon (vertical white line of *BI*), partial and complete block developed. An Adams-Stokes attack occurred. An ectopic auricular wave is present in the lower tracing.

arterial pressure. A similar dose was therefore given fourteen minutes later. One-half hour after the initial dose the systolic blood pressure had risen from 112 to 130 mm., and the diastolic pressure remained at 64 mm. The usual balloon experiment performed at this time failed to induce the Adams-Stokes attack. An analysis of the electrocardiograms revealed, however, that although the syncope was abolished, the increase in the intraballoon pressure induced complete dissociation (fig. 7). In contrast to the irregular rhythm in the control experiments, the ventricle took up a remarkably regular ectopic rhythm at a rate only slightly less than normal.

Ephedrine sulphate in doses of 23 mg. was administered at intervals of about three hours. After a total of 184 mg. had been administered within twenty-four hours, during which period the patient had no attack, the balloon experiments were performed. The results of these observations were striking. Although there was no appreciable change in the cardiac rate or in the arterial pressure, stimulation of the diverticulum by means of higher balloon pressure than usual failed to induce the Adams-Stokes attack, although the electrocardiographic trac-

ings revealed instantaneous development of heart block following inflation of the balloon (fig. 8). These observations were repeated with identical results. Thus ephedrine, as epinephrine, in well tolerated and relatively small amounts, abolished syncope but not the heart block. The effect of ephedrine manifested itself, as did epinephrine, in a prompt autonomic rhythm of the ventricular pacemaker, with a relatively high ventricular rate. This finding indicates that ephedrine in relatively small doses increases the excitability of the ventricles. The excitation

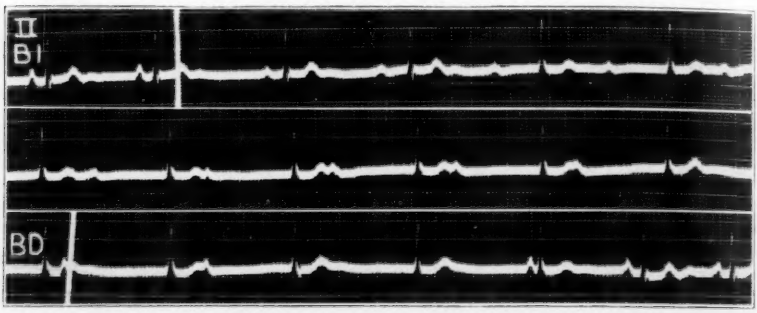

Fig. 7 (case 1).—Electrocardiogram, lead II. Continuous tracing representing the effect of epinephrine. Following inflation of the balloon (white vertical line of *BI*), partial, then complete, block followed. Note that after deflation of the balloon (white vertical line *BD*) a change of complete block to sinus rhythm occurred without the transition of partial block. The ventricular rhythm was remarkably regular throughout, and an Adams-Stokes attack did not occur.

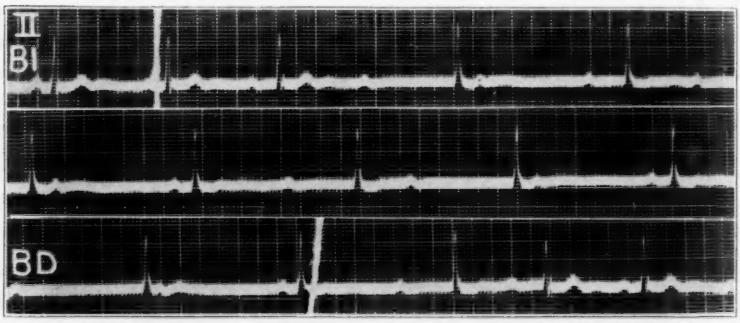

Fig. 8 (case 1).—Electrocardiogram, lead II. Continuous tracing representing the effect of ephedrine. Following inflation of the balloon (vertical white line of *BI*), complete block with regular rhythm followed. Following deflation of the balloon (vertical white line of *BD*), there was a return to normal rhythm with transient partial block. An Adams-Stokes attack did not develop.

remains concealed as long as the supranodal pacemakers dominate the cardiac rhythm, but when the function of these pacemakers is inhibited, it promptly becomes manifest. During the period that the patient took ephedrine, no spontaneous attacks developed.

Atropine sulphate in a dose of 1 mg. was administered subcutaneously, and sixteen minutes later, when no systemic effects were noted and the heart rate failed to show an appreciable elevation, the balloon experiment was repeated. No manifestation of an Adams-Stokes attack followed. The electrocardiographic tracing revealed partial block coinciding with the stimulation caused by the balloon (fig. 9). The P R intervals were from 0.28 to 0.32 second. Twenty minutes after the administration of atropine, the balloon experiment induced no symptoms, and the electrocardiographic tracing revealed a partial block with a shorter conduction time, varying from 0.21 to 0.26 second. Twenty-one minutes after the first injection of atropine sulphate 0.5 mg. more was administered, and seven minutes later inflation of the balloon failed to induce symptoms, and the electrocardiogram revealed a conduction time of from 0.17 to 0.18 second, which was shorter than that before the administration of atropine. The effect of atropine was studied in another instance with similar results. The remarkable finding in these experiments was the relatively small amount of atropine that was required to abolish the attack. In a previous study it was demonstrated that for the complete motor

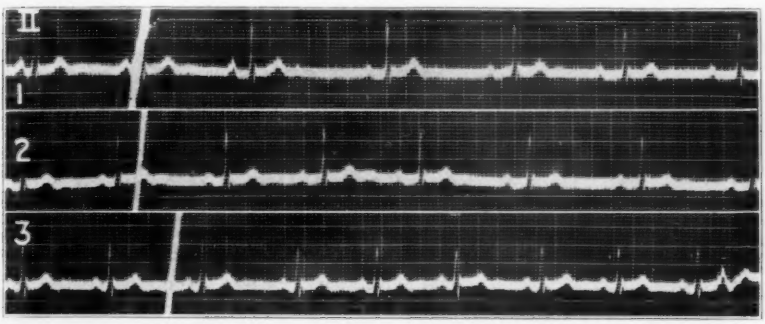

Fig. 9 (case 1).—Electrocardiogram, lead II. Successive tracings indicating the effect of the administration of atropine. Tracing *1* was obtained sixteen minutes after the subcutaneous administration of 1 mg. of atropine sulphate. Inflation of the balloon (vertical white line) induced prolongation of the P R conduction time and abolished the symptoms. Tracing *2* was obtained twenty minutes after the subcutaneous administration of 1 mg. of atropine sulphate. The prolongation of the P R interval was less. Tracing *3* was obtained twenty-eight minutes after 1 mg. and seven minutes after 0.5 mg. of atropine sulphate was administered. All of the changes were abolished.

paralysis of the vagus endings in the heart it was necessary to administer from 3.5 to 5 mg. of atropine.[1]

Reports from the patient, following discharge from the hospital, indicated that the attacks were completely controlled by the administration of one tablet of 1/120 grain (0.00054 Gm.) of atropine sulphate three times a day.

The Reflex Nature of the Syndrome.—The relation of the location of the diverticulum to the position of the vagus nerve chain, the precipitation of the

1. de Graff, A. C., and Weiss, Soma: Observations on the Extrinsic Nervous Control of the Auricles and Ventricles in Complete Auriculo-Ventricular Block in Man, J. Clin. Investigation **2**:227 (Feb.) 1926.

attack by the swallowing of food and by the distention of the esophagus and the effect of atropine in abolishing the spontaneous as well as the induced attacks suggested that stimulation of the vagus nerve was responsible for the attacks. In order to ascertain whether the attacks resulted from direct local stimulation of the motor fibers or whether they developed through stimulation of the sensory fibers of the nerve trunk sending up impulses into the medullary centers, whence motor impulses are then discharged, the following studies were devised.

After control observations with the balloon experiment had indicated the induction of the Adams-Stokes syndrome and complete dissociation of the heart, first the right and then, on another day, the left vagus nerve trunk were infiltrated with procaine hydrochloride below the level of the carotid sinus. Under these conditions repetition of the balloon experiment should continue to induce heart block if the effective stimulus acts on the motor nerve; on the other hand, the stimulation of the diverticulum should fail to induce heart block, with the path of the sensory impulses blocked, if the stimulus acts on the sensory nerve. Repeated observations following the injection of procaine hydrochloride into either of the vagus nerves revealed that heart block or syncope could not be induced when the injection was made high in the neck (fig. 10). These observations establish the reflex nature of the attacks. Since the afferent depressor nerve, as

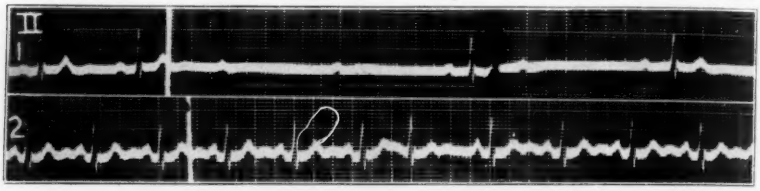

Fig. 10 (case 1).—Electrocardiogram, lead II, representing the effect of procainization of the right vagus sheath in the neck. Tracing *1*, the control, shows the usual development of block with an Adams-Stokes attack after inflation of the balloon. Tracing *2* was made after procainization. The heart rate increased, and the cardiac mechanism remained unaltered following inflation of the balloon.

well as the sensory nerve fibers of the vagus nerve, runs parallel to the vagus nerve, the question might be raised whether it is the afferent vagus nerve or the afferent depressor nerve that is active in the precipitation of the reflex. The fact that small doses of atropine abolished the heart block and syncope strongly suggests that the nature of this reflex was vagovagal rather than depressor-vagal.

The Effect of Stimulation of the Carotid Sinus and the Eyeballs.—When the vagus was anesthetized locally in the neck, the possibility that the intercarotid nerve was also anesthetized could not be ruled out. For this reason the effect of the stimulation of the carotid sinus was tested. As indicated in figure 11, this stimulation induced a slight temporary slowing of the heart rate, a finding in accord with our contention that one abnormal cardiac or vasomotor reflex, such as the carotid sinus reflex, coexists with other vasomotor reflexes that are normal.[2]

2. Weiss, Soma, and Baker, J.: The Carotid Sinus Reflex in Health and Disease: Its Rôle in the Causation of Fainting and Convulsions, Medicine **12**:297, 1933.

It may also be contended, finally, that when the vagus trunk in the neck was paralyzed with procaine hydrochloride, the simultaneous unilateral depression of the carotid sinus may have indirectly depressed the central vagus tone, and hence the stimulation of the vagus motor fibers remained ineffective. Our actual experiences with the behavior of the carotid sinus in man do not support this contention. We have demonstrated that unilateral paralysis of the carotid sinus does not interfere with the cardio-inhibitory effect of the vagus nerve when the carotid sinus of the unanesthetized side is stimulated. Indeed, in a number of instances the intensity of the cardio-inhibitory reaction and the severity of Adams-Stokes attacks became increased.[2] Just as the stimulation of the carotid sinus failed to elicit abnormal response so also did pressure on each eyeball.

The Intracardiac Mechanisms of the Onset and Disappearance of Heart Block.—This study afforded an unusual opportunity to analyze the changes associated with the occurrence and disappearance of heart block. We have therefore systematically analyzed particularly the conduction time (P R), the width of the ventricular complexes (Q R S) and the electrical systole (Q T). Between the attacks the only abnormal feature of the electrocardiogram was the occasional prolongation of the P R interval. The P R intervals varied between 0.17 and 0.24 second. These

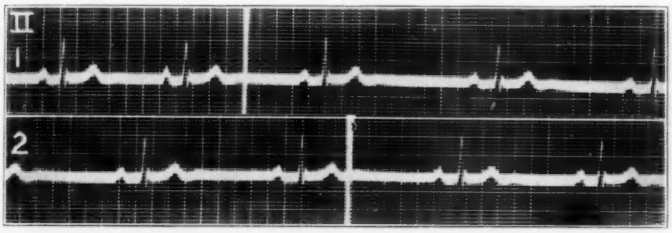

Fig. 11 (case 1).—Electrocardiogram, lead II. The continuous tracing representing the effect of pressure on the right carotid sinus. The vertical white line of the upper tracing indicates the application of pressure, and the line of the lower tracing, the release. Note the slight prolongation of the P R interval and the slowing of the heart rate. No symptoms developed.

variations were apparently related to changes in sensitivity in the reflex arc. On inflation of the balloon there usually followed from two to four beats with prolonged P R intervals, after which auriculoventricular dissociation, associated with asystoles or ectopic beats, occurred. Frequently the pressure in the balloon fell temporarily, or peristaltic movements of the esophagus gradually carried the inflated balloon away from the site of the diverticulum, and hence the dissociation was interrupted by the returning domination of a higher pacemaker. The fact that the development of complete dissociation was not instantaneous but was frequently preceded by prolongation of the P R interval was the result of gradual induction of pressure in the balloon. In a few instances, when the pressure was induced suddenly, the dissociation from the normal cardiac mechanism occurred instantaneously.

An analysis of the P R intervals with progressively increased pressure in the balloon indicated that when the intervals became prolonged up to 0.32 second, auricular impulses still got through regularly. The highest interval with ventricular response was 0.35 second. With the release of pressure, partial block first

developed, the P R interval then gradually decreasing to the normal conduction. We are unable to state whether this regular occurrence was the result of the gradual release of pressure or of fatigue of the conductive system following the vagal inhibition. With the inflation of the balloon there occurred a moderate slowing of the auricles.

Analysis of the duration of the Q R S complexes, as well as of the electrical systole (Q T), revealed no definite changes during the state of dissociation.

THE EFFECT OF EPHEDRINE ON THE BLOOD FLOW IN A CASE OF COMPLETE HEART BLOCK

Observations in case 1 indicated that following the administration of ephedrine the syncope was abolished, although the complete cardiac dissociation occurred as before. In order to throw light on the possible effect of ephedrine on the blood flow, the cardiac output in a case of complete heart block was studied on seven occasions. The rate of blood flow was measured by the acetylene method of Grollman [3] and by the optical method of Broemser.[4] In therapeutic doses similar to those administered to the patient with transient heart block, ephedrine did not change the minute or the stroke volume output of the heart. The stroke volume in this case was more than double the normal volume before and after ephedrine, which is in harmony with previous experience.[5]

THE EFFECT OF DISTENTION OF THE ESOPHAGUS

The close proximity of the vagus nerves to the esophagus suggested the necessity of control observations on the effect of distention of the esophagus. This procedure was therefore carried out, in addition, in two normal subjects, in two patients in whom fainting attacks were induced by carotid sinus pressure, and in one patient with a diverticulum of the esophagus similar in position and extent to that in case 1, but without spontaneous fainting attacks. In none of these subjects were we able to induce any cardiac slowing or symptoms of faintness or dizziness. In a study of the mechanism of visceral referred pain, Weiss and Davis [6] also reported that distention of various portions of the

3. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

4. Broemser, P., and Ranke, O. F.: Ueber die Messung des Schlagvolumens des Herzens auf unblutigem Weg, Ztschr. f. Biol. **90**:467, 1930. Lauber, H.: Ueber arterielle Blutströmung in normalem und krankhaftem Zustand. Ergebnisse einer sphygmo-manometrischen Kreislaufuntersuchung, Ergebn. d. inn. Med. u. Kinderh. **44**:678, 1932.

5. Ellis, L. B., and Weiss, Soma: Studies in Complete Heart Block: I. The Cardiac Output and the Peripheral Circulatory Mechanism, Am. J. M. Sc. **182**:195, 1931.

6. Weiss, Soma, and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain: Skin Infiltration as a Useful Therapeutic Measure, Am. J. M. Sc. **176**:517, 1928.

esophagus in a group of normal subjects was never associated with dizziness or fainting or with cardiac irregularity.

REPORT OF ADDITIONAL CASES WITH ADAMS-STOKES ATTACKS OF NERVOUS ORIGIN

In addition to case 1, studied extensively, we wish to report two cases in which the clinical and electrocardiographic observations demonstrate the development of Adams-Stokes attacks probably also of vago-vagal reflex origin. In both cases the heart between attacks was apparently normal.

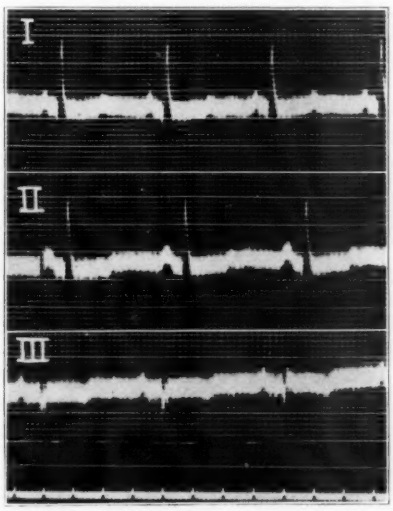

Fig. 12. (case 2).—The normal electrocardiogram, leads I, II and III.

CASE 2.—*History.*—A housewife, aged 59, was observed in the Peter Bent Brigham Hospital in 1921. She had always been in good health until ten days previous to entrance to the hospital when fainting spells developed. She had fainted about thirty times. The attacks occurred in any position, and they were precipitated usually by swallowing, by something touching a "certain spot" in the throat and by dryness of the mucous membrane of the mouth. The attacks are described in the record as follows: The patient complained of a peculiar dry sensation in the left side of the throat associated with a sharp pain radiating toward the ear. The eyes were tightly compressed. The mouth closed firmly. The patient moaned. There were marked pallor of the face and distinct slowing of the pulse. Lateral oscillation of the eyeballs was noted. The patient appeared to be in a semiconscious condition during a mild attack, complete unconsciousness characterizing the more severe attacks. As the attack progressed the pupils became widely dilated, until the iris was practically invisible, and there was no

reaction to light. Diffuse perspiration broke out over the face. Tense contractions of the arm and sometimes of the legs, hands and feet occurred. The patient breathed more rapidly. Sometimes there was a conjugate deviation of the eyes up and to the left. The pupils then returned to normal size, and the patient breathed in a normal manner.

Physical Examination.—The structures of the oral cavity appeared to be normal. The tonsils were not infected. There was marked pulsation of the right side of the neck. The lymph nodes were not palpated. The rest of the examination gave essentially normal results. Between the attacks the normal-sized heart was regular, with occasional extrasystole. During attacks the cardiac rate fell usually from 80 to 40, and the pulsations of the soft arteries could not be felt. The serologic tests and other examinations of the blood and urine did not yield pertinent information. The roentgen examination of the neck gave negative results. The electrocardiograms between attacks were normal. These attacks were precipitated by gagging the patient with a tongue depressor, by pressing the left eyeball

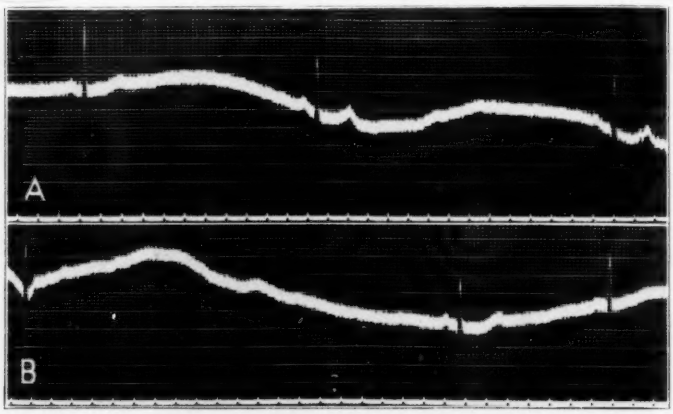

Fig. 13 (case 2).—The effect of gagging (tracing *A*) and of pressure over the left eyeball (tracing *B*). Both procedures induced marked slowing of the heart due to long sinus pauses.

and by stimulation of the vagus by pressure over the sheath. Electrocardiograms obtained during the attacks revealed markedly prolonged irregular sinus pauses up to about four seconds. No partial or complete block was present (figs. 12 and 13). Spraying of the throat with cocaine prevented the attacks, which after two weeks in the hospital showed no tendency to return. The patient was discharged improved. In April 1922, a series of similar attacks returned. Following tonsillectomy, all of the symptoms disappeared, and the patient was enjoying good health when last seen, in December 1933.

Obviously in this case, too, Adams-Stokes attacks were precipitated through a nervous mechanism in a patient who apparently had a structurally normal heart. It is of special interest that the source of attack was simple sinus slowing of the heart due to stimulation of the vagus nerve, and that the stimulation of the vagus nerve could be obtained

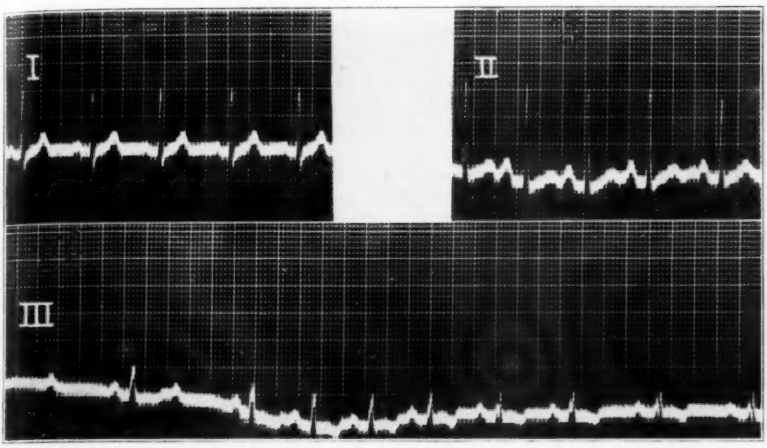

Fig. 14 (case 3).—Control electrocardiograms, leads I, II, and III. Lead III shows transient auriculoventricular block, caused probably by swallowing.

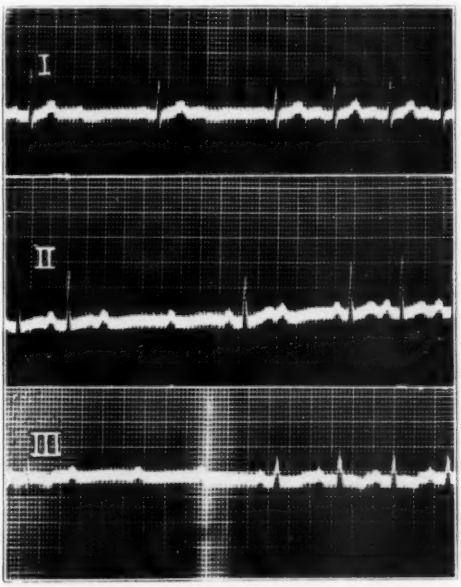

Fig. 15 (case 3).—Leads I, II and III, showing the cardiac mechanism during the swallowing of food. High grade auriculoventricular heart block was present.

probably reflexly through stimulation of a sensory branch of the eyeball or the vagus "sheath." Thus, in this case marked vagal slowing could be induced from more than one afferent nervous channel of the parasympathetic system.

CASE 3.—A woman, aged 28, was repeatedly observed by Dr. John Allen Oille of Toronto. Since the age of 2 years she had had attacks of syncope coming on particularly during meals. After 1929 the attacks appeared more frequently and at any time during the day. The patient became unconscious when playing the piano or reading or even when walking. Between attacks the results of physical examination and the electrocardiogram were normal. When the patient swallowed food the ventricle missed from one to four beats. At times, presumably when the ventricle missed more beats, she became unconscious. Electrocardiographic tracings revealed partial and complete heart block after food was swallowed (figs. 14 and 15). Atropine in doses of 1 mg. abolished block.

COMMENT

Transient and Neurogenic Heart Block.—The clinical aspect of case 1, as well as the relation of the Adams-Stokes attack to the esophageal diverticulum, is unique and, so far as we know, has not heretofore been reported. Transient complete block in association with the Adams-Stokes syndrome from any source is a relatively rare condition. In reporting a case of transient complete block in 1923, Carter and Dieuaide [7] were able to collect eight additional cases previously reported. Since that time Kahler,[8] Gager and Pardee,[9] Carter and McEachern,[10] Cheer and T'ang [11] and Gager [12] have reported cases, and these, with our two cases, make a total of sixteen that are familiar to us. In the majority of these instances the transient heart block soon changed to permanent block, and morphologic examination of the heart revealed organic lesions in the conductive mechanism or in the coronary arteries. Thus in the majority of instances the predominant underlying lesion was structural, within the heart.

Heart block of neurogenic origin is particularly rare, although in the earlier literature cases have been reported in which the source of

7. Carter, E. P., and Dieuaide, F. R.: Recurrent Complete Heart Block with Normal Conduction Between Attacks, Bull. Johns Hopkins Hosp. **34**:401, 1923.

8. Kahler, H.: Zur Kenntnis des neurogenen Adams-Stokes, Wien. Arch. f. inn. Med. **7**:207, 1923.

9. Gager, L. T., and Pardee, H. E. B.: Intermittent Complete Heart-Block and Ventricular Standstill, Am. J. M. Sc. **169**:656, 1925.

10. Carter, E. P., and McEachern, D.: Recurrent Complete Heart-Block. Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks, Bull. Johns Hopkins Hosp. **49**:337, 1931.

11. Cheer, S. N., and T'ang, T. K.: Transient Complete Heart Block with Adams-Stokes Attacks and Normal Auriculo-Ventricular Conduction Between Attacks, China M. J. **46**:1081 (Nov.) 1932.

12. Gager, L. T.: Intermittent Complete Heart Block, Virginia M. Monthly **59**:300, 1932.

the heart block was claimed to be in the central nervous system. For the most part, however, these cases were reported previous to the discovery of the cardiac-conductive system, and no adequately thorough morphologic study of the central nervous system or of the heart was performed. Moreover, it is questionable whether the findings reported in the central nervous system had any causative relationship to the heart block.

The theory that the nervous system, the vagus nerve in particular, is responsible for the Adams-Stokes syndrome is relatively old. It was first suggested in 1872 by Charcot [13] following the classic demonstration of the inhibitory effect of the vagus on the heart by the celebrated Weber brothers in 1850. Previous to the discovery of the conductive system, such lesions as softening of the cerebellar peduncle or the vagus centers, compression of the medulla oblongata or the pons and intracranial vascular varicosities were held responsible for the symptoms.[14] With the discovery of the conductive system of the heart in the beginning of the present century, however, primary structural or functional changes within the system were held to be responsible for the Adams-Stokes syndrome and for complete heart block. As organic lesions of the conductive system were demonstrated in the majority of instances, and, contrariwise, as direct clinical or experimental evidence for the neurogenic origin of heart block was lacking, the theory of the primary neurogenic etiology of the Adams-Stokes syndrome with heart block was practically discarded.

Only a few cases of heart block in which there was adequate evidence of nervous origin have been reported. In the cases of Hay,[15] Lutembacher,[16] Gallemaerts,[17] Starling [18] and Kahler,[8] the precipitating rôle of the vagus nerve was suggestive; nevertheless, the primary rôle obvious of organic lesions or of nutritional disturbances of the heart is definite. The case reported by Flaum and Klima in 1932 [14] is one of the best examples of the Adams-Stokes syndrome of nervous origin. In this instance, a patient, aged 63, previously in good health, had severe pain in the left side of the throat and neck after swallowing. On some occasions the pain was associated with syncope of from one to two

13. Charcot, J. M.: Leçons sur les maladies du système nerveux faites à la Salpétrière, Paris, A. Delahaye, 1872-1873.

14. Flaum, E., and Klima, R.: Zur neurogenen Form des Adams-Stokesschen Symptomenkomplexes, Wien. Arch. f. inn. Med. **23**:223, 1932. Kahler.[8]

15. Hay, J.: Bradycardia and Cardiac Arrhythmia Produced by Depression of Certain of the Functions of the Heart, Lancet **1**:139, 1906.

16. Lutembacher, R.: Bradycardie orthostatique. Intermittence de conduction du faisceau de His, Arch. d. mal. du cœur **12**:145, 1919.

17. Gallemaerts, V.: Dissociation auriculo-ventriculaire provoquée par l'orthostatisme (bradycardie orthostatique), Arch. d. mal. du cœur **16**:332, 1923.

18. Starling, H. J.: Heart Block Influenced by the Vagus, Heart **8**:31, 1921.

minutes in duration. Although the laryngoscopic examination gave negative results, it was found that pressure on the sinus piriformis precipitated syncope with pain identical to that which had occurred spontaneously. The authors concluded that the cardiac slowing was precipitated by the stimulation of the superior laryngeal nerve through one of the sensory nerves of the larynx. This belief was confirmed by the fact that anesthetization of the larynx abolished the attacks. Electrocardiographic studies revealed that the cardiac slowing was due to sino-auricular block. Thus, in this case, stimulation of a sensitive afferent vagus branch resulted in bradycardia with sino-auricular block. The similarity between this case and case 2 of our group is striking.

Gluch [19] reported the occurrence of the Adams-Stokes syndrome resulting from sinus arrhythmia with marked bradycardia in a case of bronchiogenic sarcoma causing paralysis of the recurrent laryngeal branch of the left vagus. Irritation of the vagus nerve by the tumor must have occurred, and the relation of the tumor to the vagus nerve was somewhat similar to that of the diverticulum in the case studied by us. In a previous communication we also recorded instances in which transient complete heart block with the Adams-Stokes syndrome was induced through stimulation of the carotid sinus.[2] In these cases complete heart block resulted from a reflex stimulation. The afferent portion of this reflex reached the medullary centers through the intercarotid nerve, motor impulses then being discharged from the vagus center to the heart. One of us (Dr. Weiss) [20] gave evidence that cardiac slowing induced by digitalis is due in part to a vagovagal reflex rather than to local stimulation of the vagus endings. These clinical and experimental experiences were the basis for the belief that "motor stimulation of the vagus depends, at least in the majority of instances, on reflex stimulation." [2] The demonstration (case 1) of the fact that even in direct mechanical stimulation of the vagus nerve sensory rather than motor impulses are set up further substantiates this belief. Recent experimental evidence for the reflex nature of vagal stimulation in animals is not lacking.[21] Thus Adams-Stokes syndrome caused by bradycardia is at times not only neurogenic but reflex in origin. The nature of the bradycardia can be simple sinus arrhythmia, sino-auricular block or complete auriculoventricular block.

19. Gluch, B.: Elektrokardiographische Beobachtungen bei dem Morgagni Adams-Stokes'schen Symptom-Komplex, Ztschr. f. Kreislaufforsch. **24**:561 (Sept. 15) 1932.

20. Weiss, Soma: The Effects of the Digitalis Bodies on the Nervous System: An Analysis of the Mechanism of Cardiac Slowing, Nausea, and Vomiting, Psychosis, and Visual Disturbance Following Digitalis Therapy, M. Clin. North America **15**:963, 1932.

21. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, London, H. K. Lewis & Co., 1929.

The spontaneous fluctuations in the basal cardiac rate, in the auriculoventricular conduction time and in the arterial blood pressure in our case suggest that the parasympathetic tone varied from day to day, depending presumably on the local process within the diverticulum and on the general bodily state of the patient. Such daily variations in the vagal tonus offer an explanation as to why the spontaneous attacks of syncope, as well as the attacks induced experimentally, developed more easily at one time than at another.

In certain cases with primary organic disease within the heart,[22] a superimposed increased vagal tonus has played a precipitating rôle in the development of the complete auriculoventricular dissociation. In other instances, with only incomplete severance of the conductive system by local organic lesions, a combination of added insufficient coronary circulation and depression of the remaining functioning conductive system by bacterial toxins or drugs has played a precipitating rôle. Thus multiple causes rather than a single cause are often responsible for the development of the transient auriculoventricular dissociation. The results of the study of our case nevertheless indicate that the primary and dominating factor was sensory irritation of vagal afferent fibers. No evidence for the existence of secondary factors was available. The remarkable fact that the attacks have recurred over a period of ten years without change in character and with only slight increase in tendency also supports this contention. Thus, the appearance of the Adams-Stokes syndrome does not always, as is generally believed, offer a bad prognosis. It does so usually because in the vast majority of instances the syndrome is an indication of severe organic heart disease.

The Mechanism of Syncope.—The onset of syncope occurred in from fifteen to thirty seconds after the induction of heart block described here. Obviously the duration of the asystole and the ensuing cerebral ischemia were determining factors. In several of the attacks it was noted, however, that the arterial pressure during the syncopal attack was lowered only slightly, while during the onset of heart block after the administration of ephedrine, when the cardiac rhythm was regular and no syncope developed, the degree of fall in the arterial pressure was greater. It appears, then, that a sudden stoppage or slowing of the blood flow, even with maintained blood pressure, was a more active factor in the precipitation of an Adams-Stokes attack than was a slow, regular rhythm or fall in arterial pressure. The experience of sudden dizziness and sensation of faintness, associated with the occurrence of a single premature beat, also supports this contention. In a previous study of the cerebral circulation in fainting and convulsions following stimulation of the carotid sinus, we brought forward evidence showing that in the precipitation of cerebral symptoms, the rate of

22. Kahler.[8] Starling.[18]

change from the normal state to an ischemic state rather than the absolute degree of ischemia plays a dominant rôle.[2] Obviously, in the pressure of an inelastic and sclerotic vascular system, the same degree of asystole will result in a greater degree of cerebral ischemia. Through excitation of vascular reflexes, an active constriction or dilatation of the cerebral blood vessels may also occur which can further accentuate or diminish, respectively, the degree of ischemia. It has also been shown that vasomotor and circulatory changes associated with changes in the bodily posture also have an important bearing on the rate of development of cerebral ischemia.[2]

Often it is difficult to differentiate between the ischemia resulting from the cardiac irregularity and that resulting from the simultaneous activity of other vasomotor reflexes. It is known, for example, that the arterial blood pressure and the vasomotor state may show considerable periodic fluctuation in the different stages of Cheyne-Stokes breathing. Syncope occurs at the apneic stage even without appreciable slowing of the heart. In other instances, however, the apneic stage is associated with marked slowing of the heart rate as a result of simultaneous sinus bradycardia or of temporary partial or complete block due to a rhythmically shifting pacemaker. In such instances it is difficult to evaluate the relative rôles of the primary vasomotor changes and the cardiac ischemia. That in some of these instances the vasomotor rather than the cardio-inhibitory factor predominates is shown by the fact that the appearance of early symptoms of Adams-Stokes attacks in such cases may precede the onset of cardiac slowing.[23] It is the various combinations of these factors that result in marked differences in the time of onset of syncope. Thus, ventricular standstill varying from six to sixty-seven seconds in duration has been reported to occur before the onset of convulsive movements.[9]

In a study of the interaction between the emotional states and the cardiovascular system, it was pointed out that clinical evidence suggests that certain sensations such as anxiety and nervousness have their origin in the heart and particularly in coronary disease.[24] Other clinical manifestations also indicate that certain features of the Adams-Stokes syndrome may be due to sudden disturbances of some at present unrecognized nervous connection between the heart and the central nervous system. Thus in the precipitation of syncope of the Adams-Stokes type, in addition to the factor of general ischemia, other factors, particularly reflexes, play an important rôle.

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23. Weiss, Soma: Unpublished observations.

24. Weiss, Soma: The Interaction Between Emotional States and the Cardiovascular System in Health and in Disease, Emanuel Libman Anniversary Volume, New York, International Press, 1932, vol. 3, p. 1181.

The Comparative Value of Drugs.—A comparison of the efficacy of the therapeutic agents used shows that while barium chloride was without effect or was only slightly beneficial, ephedrine, epinephrine and atropine abolished the Adams-Stokes attacks. Atropine prevented the block; ephedrine and epinephrine abolished the irregular periods of asystole attending the onset of block but did not prevent the block. The beneficial effect of ephedrine in small doses is particularly significant, as this drug can be taken orally without unpleasant secondary effect. Our observations suggest that ephedrine, when administered in doses which do not raise the rate of sinus rhythm, increases the excitability of the ventricles. Contrary to experience in other diseases, in the type of Adams-Stokes attack described, ephedrine can be used more advantageously than epinephrine. The use of ephedrine in an Adams-Stokes attack has been advocated in recent years;[25] barium chloride, on the other hand, after a claim for its beneficial effect[26] has been found repeatedly ineffective.[27] We found that it was ineffective in four cases of heart block with Adams-Stokes attack.[23] We did not use digitalis in the study, because it increases the vagal tone, and hence it was feared that it might increase the severity of the spontaneous and induced attacks.

Our experiences with these drugs are not necessarily applicable to the Adams-Stokes attacks in patients with permanent block. In such instances the prevention of a low cardiac rate with resulting decreased blood flow is the chief therapeutic aim. As the vagus control over the ventricles is to a large extent ineffective in the presence of complete permanent block, atropine usually is of slight or no beneficial effect, and digitalis is of questionable usefulness. Thus the medication of choice in these cases, too, is ephedrine and epinephrine.

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25. Hollingsworth, M.: Ephedrin in Adams-Stokes Syndrome, California & West. Med. **26**:802, 1927. Stecher, R. M.: A Note on Stokes-Adams Disease Treated with Ephedrin, Am. Heart J. **3**:567 (June) 1928. Parade, G. W., and Voit, K.: Zur Adrenalin- und Ephetoninbehandlung der Adams-Stokesschen Krankheit, Deutsche med. Wchnschr. **55**:179, 1929. Wood, J. E., Jr.: Treatment of Adams-Stokes' Syndrome with Especial Reference to the Use of Ephedrine, South. M. J. **25**:927, 1932. Roberts, L. J., and Taber, T. H.: Ephedrine in the Treatment of Adams-Stokes Syndrome. Report of Case, U. S. Nav. M. Bull. **31**:27, 1933.

26. Cohn, A. E., and Levine, S. A.: The Beneficial Effects of Barium Chlorid on Adams-Stokes Disease. Report of Three Cases, Arch. Int. Med. **36**:1 (July) 1925.

27. Heard, J. D.; Marshall, W. R., and Adams, F. S.: Heart-Block with Convulsive Syncope: Case Report and Pathological Findings in a Patient Unsuccessfully Treated with Barium Chloride, Am. Heart J. **2**:562, 1926-1927. Parsonnet, A. E., and Hyman, A. S.: Barium Chlorid in the Stokes-Adams Syndrome of Complete Heart Block: Negative Results in Eight Cases, Am. J. M. Sc. **180**:356, 1930.

SUMMARY AND CONCLUSIONS

1. This study centers around observations on a patient who for ten years suffered from attacks of fainting precipitated usually by the swallowing of food. The patient had a traction diverticulum of the esophagus, distention of which with the aid of a rubber balloon promptly induced auriculoventricular dissociation of the heart and syncope. The release of pressure in the balloon was associated with a prompt return of normal sinus rythm and the disappearance of symptoms.

2. Distention of the esophagus of normal subjects and of patients with syncope due to hyperactivity of the carotid sinus failed to induce fainting or change in the cardiac rhythm.

3. Barium chloride failed, not only to influence the severity and the frequency of syncope, but also to prevent the development of heart block. Epinephrine and ephedrine in small doses, which induced no change in the arterial pressure and only slight elevation in the heart rate, abolished all of the symptoms, although pressure on the diverticulum continued to induce complete heart block. Following the administration of epinephrine and ephedrine, the onset of idioventricular rhythm, in contrast to the control observations, was associated with remarkably regular rhythm as a result of increased excitability of the ventricles. Atropine in doses which produced only slight depression of the vagal motor endings abolished the symptoms as well as the heart block. Paralysis of either of the vagus sheaths in the neck with procaine hydrochloride also abolished the fainting and the block.

4. The Adams-Stokes attack in this case was induced by heart block precipitated by a vagovagal reflex. The source of the reflex was irritation of the sensory endings of the vagi by the diverticulum.

5. The intracardiac mechanism active at the onset and the disappearance of heart block of reflex origin are described.

6. The cardiac output and other aspects of the hemodynamics in a case of complete heart block were studied with the acetylene and optical methods. Ephedrine failed to induce a significant change in the blood flow.

7. The relative rôle of organic cardiac lesions and of neurogenic factors in the precipitation of Adams-Stokes attacks with heart block is discussed, and the simultaneous presence of multiple etiologic factors is stressed.

8. In addition to the three cases of vagovagal reflex origin presented here, and to those due to hyperactive carotid sinus, previously reported, there are only two cases of the Adams-Stokes syndrome familiar to us in which changes in the cardiac rhythm were primarily of vagal origin.

In this group with neurogenic Adams-Stokes attacks the precipitating cardiac mechanisms were sinus pauses, sino-auricular block, partial and complete block and total cardiac standstill.

9. It has been demonstrated that abnormal hyperactivity of the vago-vagal reflex can be associated with a normal state of other reflexes of the same type.

10. In the precipitation of Adams-Stokes attack, cerebral ischemia due to decreased cardiac output is only one factor. The rôle of other factors, particularly of vasomotor reflexes, is emphasized.

Dr. Henry A. Christian and Dr. Samuel A. Levine permitted us to include in this study case 2, observed in the Peter Bent Brigham Hospital, and Dr. John Allen Oille permitted us to describe case 3.

THE HEART AND GREAT VESSELS IN COMBINED SYPHILITIC AND RHEUMATIC INFECTION

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Two diseases, the cause of cardiac dysfunction, syphilis and rheumatic fever, are seldom reported as associated in studies of these two diseases. Cowan and Rennie,[1] in a study of one hundred and four patients suffering from disease of the aortic valves, found definite rheumatic disease of the mitral valve in 3.1 per cent of those with syphilis of the heart. Cotton [2] found among fifty patients with aortic insufficiency with an average age of 31 years that 2 per cent gave a history of syphilis. Fordyce [3] reported nine cases of children with rheumatic heart disease with a severe course in whom asymptomatic congenital syphilis was discovered. The contribution of Von Glahn and Wilshusen [4] included the pathologic study of two cases of recent rheumatic myocarditis superimposed on syphilitic aortitis. In the Joseph Sailer Cardiac Clinic of the Philadelphia General Hospital, four cases of frank rheumatic heart disease with a superimposed infection of syphilis were found in a series of nine hundred and twenty-three patients. In these four, the rheumatic infection was clinically quiescent, and remained so through the entire course of antisyphilitic therapy. In the fourth case, one of neurosyphilis with rheumatic mitral disease, the spinal fluid was persistently resistant to treatment.

In one thousand and thirty-one autopsies performed at the City Hospital between Jan. 1, 1927, and Oct. 1, 1931, seventy-one (exclusive of aneurysm) were on syphilitic patients with clinical heart disease. Of this group, eight were found with rheumatic heart disease. Six hearts of this group were available for study and form the basis for this report.

Read before the Section on General Medicine of the College of Physicians, Philadelphia, Feb. 27, 1933.

From the Department of Pathology and the Electrocardiographic Laboratory of the Medical Services, City Hospital, Welfare Island, Department of Hospitals.

1. Cowan, J., and Rennie, J. K.: Syphilis of the Heart, Brit. M. J. **2**:184, 1921.

2. Cotton, T. F.: Observations of Aortic Disease in Soldiers, Lancet **2**:470, 1919.

3. Fordyce, A. D.: Undetected Syphilis in Rheumatic Infection in Children, Brit. M. J. **1**:530, 1930.

4. Von Glahn, W. C., and Wilshusen, H. J.: Syphilitic Aortitis and Acute Rheumatic Myocarditis, Proc. New York Path. Soc. **24**:71, 1924.

REPORT OF CASES

CASE 1.—S. P., a Negress, 16 years old, a schoolgirl, was admitted to the City Hospital on May 27, 1927, because of sore throat, painful joints, a rash on the body and dyspnea. At the age of 11, she had chorea; at 13, pertussis. She had always been subject to sore throat. Nine months previously, she had an attack of poly-

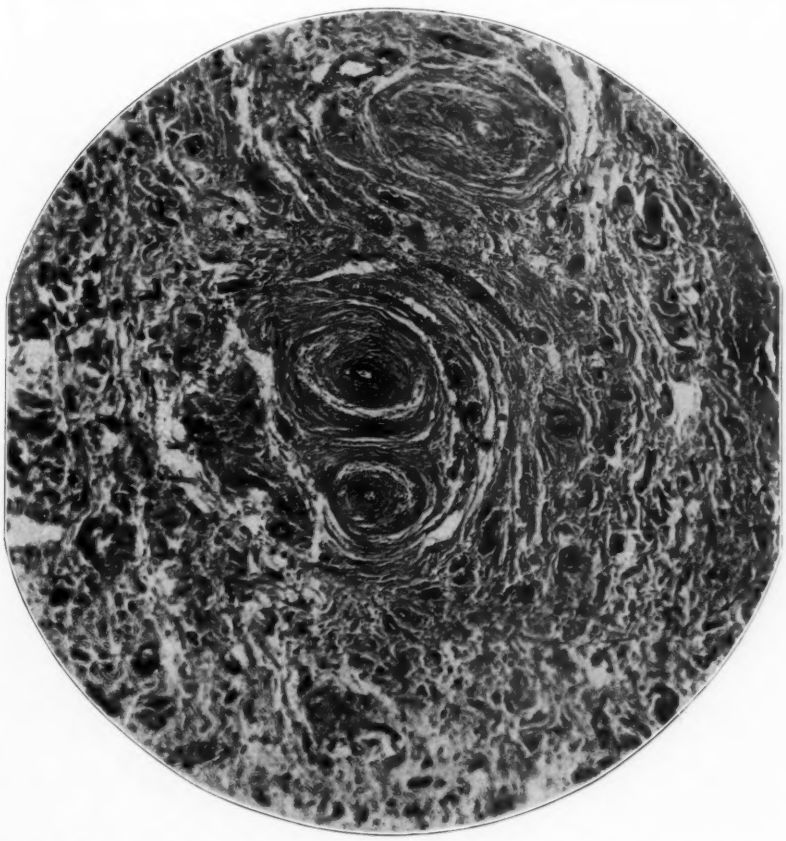

Fig. 1.—Endarteritis of the vasa vasorum in the commissural region; a lesion found in five of the cases.

arthritis. Some weeks later, during an examination previous to tonsillectomy, a cardiac lesion was discovered. Early in 1927, there was cardiac decompensation, but recovery was prompt. Shortly afterward, following exposure, she contracted a genital sore which did not heal.

On physical examination the patient was moderately orthopneic. The pupils were slightly unequal, but responded to light and in accommodation. There were

a generalized rash on the body, mucous patches on the mouth, a chancre on the left labium, condylomas and general adenopathy. The precordium bulged. Percussion revealed the heart to be greatly enlarged. There was a thrill with a loud blowing to-and-fro murmur over the precordium. Thrill and pistol shot sounds were present over the carotid, brachial and femoral arteries. There was a booming systolic murmur over the aortic area; the aortic second sound was absent. The liver was palpable. The blood pressure was 120 systolic and 30 diastolic. No type of cardiac pain was present. A Wassermann test of the blood showed a reaction of 4 plus. Under treatment with bismuth, salicylates and rest she improved and compensation was restored. She was discharged improved on July 10, and was referred to the clinic for further treatment.

The second admission was three days, later, with decompensation. With the exception of syphilitic lesions of the skin and mucous membranes, the condition was the same as previously. The pupils were normal. The response to therapy was slower, and compensation was not restored until October, when the mother insisted on taking her home against advice.

The third admission was on Jan. 23, 1928. Compensation continued until December, when decompensation recurred. She was extremely dyspneic, orthopneic and had generalized edema. The heart was regular, with a rate of 140. There were a presystolic thrill, shock and a harsh to-and-fro murmur at the apex. There were a pericardial friction rub, visible pulsation of the vessels of the neck and a thrill over the carotid arteries. Ascites was present. The blood pressure was 158 systolic and 35 diastolic. The white blood cell count was 13,000, with 82 per cent polymorphonuclears. The urine contained large amounts of albumin and many casts. The Wassermann reaction was negative. The temperature was from 98 to 100 F., the pulse rate from 112 to 140 and the respiratory rate from 28 to 46.

The roentgen examination showed marked enlargement of the left ventricle, enlargement of the right ventricle, marked enlargement of the left auricle (showing as a double shadow on the right side) [5] and enlargement of the auricle. The aorta was not dilated.

The electrocardiogram showed normal sinus rhythm, simple tachycardia, prolonged auriculoventricular conduction time and no axis deviation. There was slurring of the ventricular complexes.

Death occurred three days after the third admission.

The clinical diagnosis was: rheumatic pancarditis; mitral stenosis and insufficiency, and aortic stenosis and insufficiency. The anatomic diagnosis was: rheumatic pancarditis; acute interstitial myocarditis; recent pulmonary infarction; general chronic passive congestion; anasarca, and syphilis of the aorta.

The case was predominantly one of rheumatic fever with a typical history, physical findings and clinical course, with first decompensation preceding syphilitic infection, poorly sustained compensation despite therapy and death from congestive failure, complicated by superimposed acute myocardial infection of undetermined etiology.

CASE 2.—S. F., a Puerto Rican woman, aged 26, was admitted to a hospital on Jan. 25, 1928, because of dyspnea, precordial pain and edema of the ankles. She had always been subject to sore throat. She had never been pregnant. She was well until one year previously, when she had an attack of acute polyarthritis which confined her to bed for six months. In October 1927 she first suffered precordial

5. Nichols, C. F., and Ostrum, H. W.: Unusual Dilatation of the Left Auricle, Am. Heart J. **8**:205, 1932.

pain and swelling of the feet. She was in a hospital for five weeks and was discharged improved. Early in January 1929 the same symptoms recurred, and she entered a hospital. Physical examination showed a marked precordial heaving impulse, the apex beat in the sixth interspace in the midaxillary line and the right border 3 cm. to the right of the midsternal line. There was a short presystolic crescendo murmur and a loud systolic murmur at the apex. The pulmonic second sound was greater than the aortic second sound. The liver was enlarged, extending three fingerbreadths below the costal margin, and was tender. The Wassermann reaction was 4 plus.

Fig. 2 (case 2).—Posterior view of the heart. The tricuspid valve (*B*) and the mitral valve (*C*) have stenotic rheumatic lesions. The superior cava (*A*) is thrombosed, the thrombus extending down into the auricle. The probe indicates the mouth of the vessel.

On entering the City Hospital, there was a slight presystolic thrill at the apex and diastolic shock. There was a systolic murmur at the aortic area. There were frequent extrasystoles. The blood pressure was 130 systolic and 70 diastolic. The liver was just palpable. The Wassermann reaction was 4 plus.

On February 6, she complained of chills, fever, sore throat and pains in the neck and chest. The temperature was 102 F., the pulse rate 120 and the respiratory rate 32. The throat was red and injected, and the glands on both sides of the

neck were painful. The observations on the heart were unchanged. The liver was larger and tender. The white blood cell count was 15,000, with 85 per cent polymorphonuclears. By February 10 she had improved, and the temperature had returned to normal. It was not until some days later that the size of the liver decreased and the tenderness disappeared. Ten cubic centimeters of tincture of digitalis was administered from January 26 to January 31.

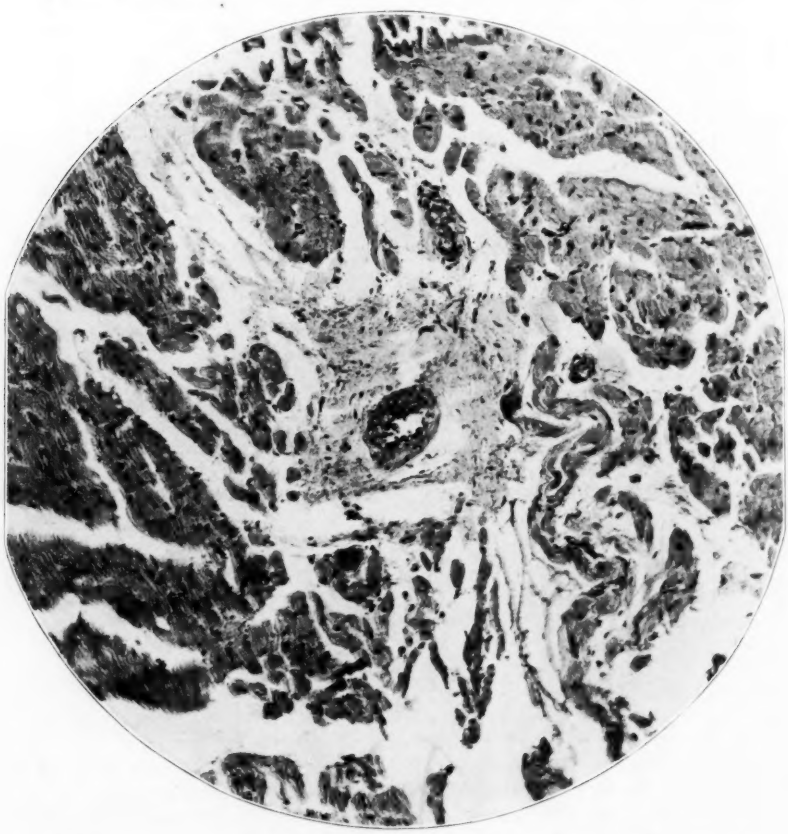

Fig. 3.—Intrinsic arteries with marked sclerosis. In case 3 the lesion was diffuse; in case 5, focal.

In the latter part of February and early March she had several attacks of precordial pain, dyspnea and vomiting. These attacks were usually accompanied by a rise in temperature from 100 to 101.8 F. Once the temperature fell to 96.4 F. These episodes lasted for two to three days. About the middle of March she had a severe pain in the right leg which persisted for three days. A few days later she had a severe pain in the left side of the chest followed by a slight cough.

The first heart sound was muffled, followed by a soft blowing systolic murmur. At the aortic area there was a soft blowing to-and-fro murmur. The pulmonic second sound was much accentuated. A pericardial friction rub was present to the left of the sternum. The liver became enlarged and tender again, and the ankles edematous. Râles developed at the bases of the lungs. Venous congestion of the neck was absent. Twenty-four cubic centimeters of tincture of digitalis was given between February 1 and March 26, inclusive. Until April the precordial pain recurred frequently, but varied greatly in intensity. The temperature varied from 98.6 to 102.6 F. By April 5 the clinical improvement was marked; the physical signs remained practically unchanged. Later in the month, a rise in temperature occurred which lasted for three days; the calves were tender to slight pressure but revealed no abnormalities. The patient was given 74 cc. of tincture of digitalis between April 10 and May 8. Attacks of paroxysmal auricular fibrillation developed with a ventricular rate of 80. Following the appearance of fibrillation, the administration of digitalis was discontinued, and the heart returned to its normal sinus rhythm, with a rate of 107. These attacks of paroxysmal auricular fibrillation recurred for a period of hours to a few days. Dyspnea was extreme, but was not accompanied by cyanosis. The systolic blood pressure remained at 120 mm. of mercury; the diastolic pressure was difficult to obtain. The temperature rose to 102 and 103 F., returning to normal between the attacks of pain and dyspnea. The liver increased rapidly in size and pulsated. At one time pain was elicited over the spleen. Following one attack of severe pain in the left shoulder and axilla, a massive swelling of the arm rapidly appeared, extending up into the neck and later into the right arm. A cordlike mass was palpable on the left side extending up into the neck. General edema developed with cyanosis. The harsh character of the cardiac murmurs appeared from time to time. Death occurred in congestive failure on July 22.

Roentgen examination showed marked enlargement of the left auricle (appearing as a double shadow on the right border of the heart), left ventricular enlargement and right ventricular enlargement. The right auricle was moderately enlarged. The main branches of the pulmonary vessels were widened. The base of the aorta was not widened, although later it was definitely widened, showing the shadow of the superior vena cava to the right of the aorta.

Electrocardiographic study showed: normal sinus rhythm, with one tracing of paroxysmal auricular fibrillation following poisoning with digitalis; normal sinus rhythm in a later tracing after digitalis was discontinued; diphasic T waves in leads 1 and 2 with a constantly inverted T wave in lead 3, and slurring of the ventricular complexes.

The clinical diagnosis was: chronic rheumatic endocarditis; mitral stenosis, and thrombosis of the subclavian veins. The anatomic diagnosis was: chronic rheumatic endocarditis, thromboses of the superior vena cava and tributaries; mural thromboses of the tributaries of the superior mesenteric vein and of the portal vein; thrombosis of the splenic vein; old and recent pulmonary thromboses; general passive congestion, and syphilis of the aorta.

This case was one of rheumatic infection with a severe course and widely scattered venous thromboses. The syphilitic element was asymptomatic.

Case 3.—F. B., a Negro, 34 years old, was admitted to the City Hospital on May 16, 1928, because of dyspnea, pains in the joints and edema of the legs. At the age of 23, he had a chancre; one year later, an attack of acute polyarthritis, and one year later, acute gonorrhea.

On physical examination he appeared acutely ill, and was moderately dyspneic. The pupils were normal, the pharynx was injected and the cervical glands palpable. Percussion revealed enlargement of the heart. A short presystolic, a systolic and a diastolic murmur were present at the apex. The pulmonic second sound was louder than the aortic second sound. The blood pressure was 120 systolic and from 50 to 0 diastolic. The liver was tender and was enlarged two fingerbreadths

Fig. 4.—In the perivascular connective tissue is a group of Aschoff cells, indicated by the arrow.

below the costal margin. The spleen was palpable and tender. The Wassermann reaction was 4 plus. The urine was normal. The temperature varied from 97 to 100 F. The patient was discharged on July 9, much improved.

The second period of hospitalization was from August 6 to Feb. 14, 1929. For two weeks after leaving the hospital he remained well. Then there occurred a sudden onset of substernal pain and shortness of breath. The pupils were normal.

The fundi revealed sclerotic vessels. At the apex was a loud systolic, a long diastolic and a suggestive presystolic murmur. The pulmonic second sound was much accentuated and louder than the aortic second sound. There was a long diastolic murmur at the aortic area. The aortic second sound was present, but faint. The blood pressure was 110 systolic and 80 diastolic. The Wassermann reaction was 4 plus. The urine was normal. The temperature was normal. The

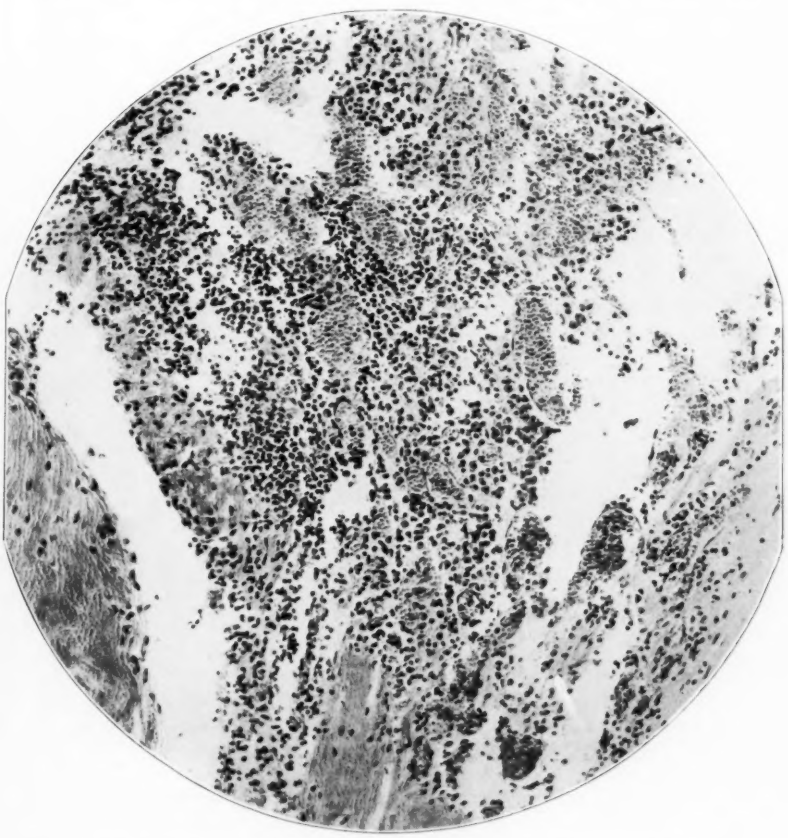

Fig. 5 (case 6).—The inflammatory lesion of the aorta at the base.

patient was fairly comfortable and compensation was good until the latter part of November. From that time until he left the hospital he had many attacks of paroxysmal dyspnea accompanied by a sensation of choking, usually with pain and usually nocturnal, sometimes diurnal. At first the attacks were not frequent, but at times several would occur in a twenty-four hour period. A distinct diastolic and a loud blowing systolic murmur were heard at the aortic area on some occasions. Once he had acute pharyngitis and adenitis, and a pericardial friction was detected.

From November onward the temperature varied from 98 to 100 F. The pulse rate varied from 110 to 120, being higher proportionately than the temperature. On discharge he was quite comfortable.

The third admission was on May 7, 1929. In April, the attacks of palpitation and dyspnea recurred, and he became very short of breath. He was distinctly orthopneic. Percussion revealed the heart larger than on the previous admissions. A thrill was present over the entire precordium. There were a loud systolic and a presystolic murmur at the apex. The aortic region was normal. The pulmonic second sound was greater than the aortic second sound. The blood pressure was 98 systolic and 62 diastolic. The Wassermann reaction was 4 plus. The urine had a specific gravity of 1.014 and a few casts. The liver was large and tender. The temperature until death, on May 16, was slightly irregular. The outstanding symptom was frequent attacks of paroxysmal dyspnea, some attacks accompanied by precordial pain. Death occurred suddenly.

The roentgen examination revealed enlargement of all the chambers of the heart. The base of the aorta on May 18, 1928, was not widened. Widening of the aorta was seen on August 18. The pulmonary fields showed evidence of chronic pulmonary stasis with secondary fibrosis. The main branches of the pulmonary vessels were widened.

Electrocardiographic study showed: normal sinus rhythm, auriculoventricular conduction time top normal (0.2 seconds); a diphasic T wave in lead 2 in one tracing, and no definite evidence of coronary disease in the T wave deflections. The ventricular complexes showed slight slurring. No axis deviation to right or left was present, but a large S wave was present in both tracings taken.

The clinical diagnosis was: rheumatic pancarditis; mitral stenosis and insufficiency; pulmonary tuberculosis, and syphilis. The anatomic diagnosis was: chronic rheumatic endocarditis; diffuse sclerosis of the intrinsic coronary arteries, and syphilis of the aorta.

This case was one of latent rheumatic infection which became evident after a syphilitic infection, progressing slowly, with the development of disease of the small vessels of the coronary system, which dominated the clinical course during the last few months.

Case 4.—J. M., a man, 37 years old, was admitted to the City Hospital on Jan. 3, 1928, because of abdominal swelling and shortness of breath. A history of syphilis and rheumatic fever was denied. He was well until one year previously, when he had lobar pneumonia. Since then he had had a chronic cough, at times with a blood-streaked sputum, and later gradually increasing dyspnea and swelling of the abdomen. He was hospitalized in December 1927. Examination at that time showed marked orthopnea and dyspnea, arcus senilis, and pupils fixed to light and in accommodation. There was dulness at the bases of both lungs, with enlargement of the heart, the apex being in the sixth interspace in the anterior axillary line. The heart sounds were diminished in intensity. The blood pressure was 130 systolic and 90 diastolic. The Wassermann reaction was negative. There were 18,000 white blood cells with 77 per cent polymorphonuclears. On fluoroscopy the aortic area was seen to be widened.

For three weeks before admission he had gradually increasing dyspnea. He was moderately comfortable. There were signs of moderate decompensation and ascites. The blood pressure was 105 systolic and 75 diastolic. The Wassermann reaction was 4 plus. The heart sounds were weak, and the heart rate 120. The second sound was replaced by a loud murmur filling the entire diastole. The liver

was enlarged to the umbilicus and was tender; a fluid wave was present. The fingers were clubbed. The eyegrounds showed marked sclerosis. The urine, at first normal, later showed large amounts of albumin, casts and white blood cells. The patient remained moderately comfortable until January 25, when his temperature rose to 103 F. with signs of lobar pneumonia. He died three days later, on January 27.

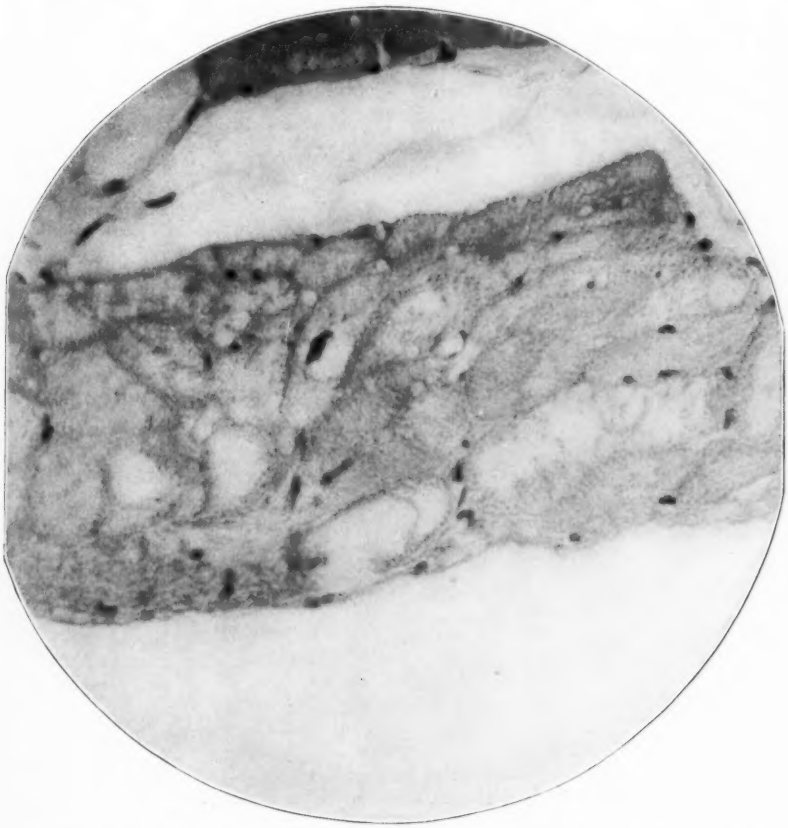

Fig. 6 (case 6).—Left branch of the conduction system, showing the marked edema of the fibers. At the edge of the section is a small portion of the cardiac muscle.

Roentgen examination showed moderate enlargement of the chambers of the heart, with slight sclerosis of the aorta, engorgement of the pulmonary vessels and evidences of chronic pulmonary infection.

Electrocardiographic study showed normal sinus rhythm, tachycardia, a low voltage T wave and slurring of the ventricular complexes. The clinical diagnosis

was: rheumatic heart disease; chronic endocarditis; mitral stenosis and insufficiency; syphilitic aortitis, and acute lobar pneumonia. The anatomic diagnosis was: chronic rheumatic pancarditis; syphilis of the aorta; chronic passive congestion; healed tuberculosis, and acute lobar pneumonia.

This was a case of a mildly decompensated rheumatic heart with syphilis of the aorta, in which an intercurrent infection developed which caused death.

CASE 5.—L. G., a white man, aged 44, was admitted to the City Hospital on April 25, 1929. At the age of 33 he contracted syphilis. At 34 he had an attack

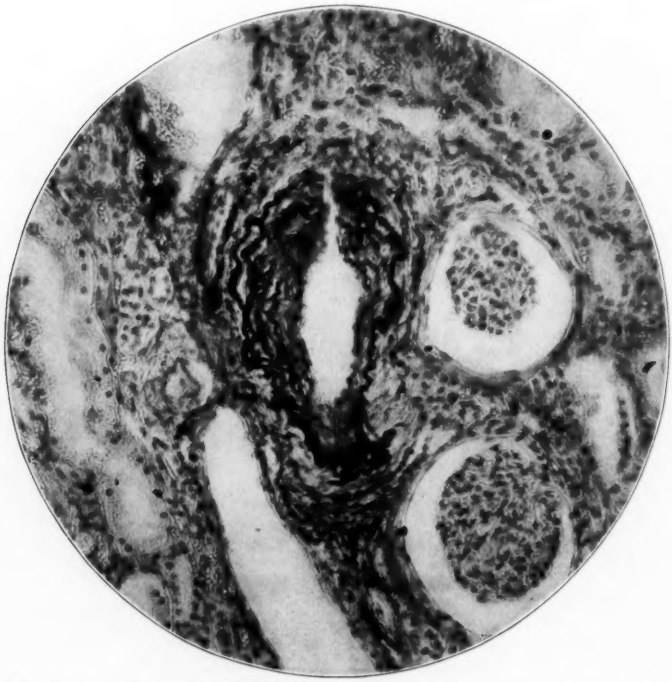

Fig. 7 (case 5).—Arterial lesion in the kidney. The photomicrograph shows the splitting of the internal elastica of an interlobular artery.

of polyarthritis. He remained well until December 1928, about nine years later. He entered the hospital because of dyspnea and precordial pain on exertion. The Wassermann reaction was 4 plus. He remained in the hospital about two weeks and then resumed his work as a laborer. For almost three months he remained well, but late in March, pains in the left side of the chest recurred, with swelling of the abdomen and legs.

On readmission to the City Hospital the physical signs were ascites, edema of the legs, venous pulsations of the vessels of the neck, dulness at the base of the right lung and râles. There was a blowing systolic murmur at the apex and a totally irregular pulse. The liver was four fingerbreadths below the costal

margin. The Wassermann reaction was 4 plus. There was again congestive failure. A loud blowing systolic murmur was heard over the entire precordium. The apex beat was diffuse in the sixth interspace in the anterior axillary line. There was no thrill or diastolic murmur. The aortic second sound was moderately accentuated, roughened and snapping. The pulse rate was 60 and totally irregular, and the blood pressure was 115 systolic and 75 diastolic. The liver was one fingerbreadth below the costal margin. The fingers were clubbed and cyanosed. The Wassermann reaction was 4 plus. The pupils were normal. For a few days, the temperature was irregular, ranging from 100 to 101 F., and then dropped to 97.8 F.

Late in May he had a few attacks of paroxysmal dyspnea. He was given 34 cc. of tincture of digitalis between May 31 and June 11. Complete heart block developed. By June 20, after the discontinuance of digitalis, the heart returned to its usual rhythm of auricular fibrillation. The blood pressure had risen to 135 systolic and 65 diastolic. There was a double murmur at the apex. The patient remained fairly comfortable until February, but climbing stairs always caused moderate dyspnea. The blood pressure gradually rose to 146 systolic and 65 diastolic. During February he had several attacks of precordial pain and dyspnea. Frequently the pain was cramplike. Occasionally, similar pain was present in the legs and abdomen. The liver was enlarged, and became tender. At times dyspnea was severe, and he would sit on the side of the bed for relief. Many of the attacks were nocturnal. The heart rate remained slow but pulse deficit appeared. During March, cyanosis became marked, and the attacks of dyspnea were extremely frequent both day and night. The blood pressure dropped to 130 systolic and 90 diastolic. Congestive failure increased, and he died on March 5.

The roentgen examination showed: marked left ventricular enlargement, enlargement of the right ventricle, definite widening of the main branches of the pulmonary vessels and enlargement of the right and left auricles. The base of the aorta was not widened.

The electrocardiographic study demonstrated the change from auricular fibrillation to complete heart block with auricular fibrillation and return to chronic auricular fibrillation, with a slow ventricular rate of 60. The T wave was diphasic in leads 1 and 2, and the T wave in lead 3 became permanently inverted. The Q R S complex was slurred.

The clinical diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, and syphilitic heart disease. The anatomic diagnosis was: healed rheumatic endocarditis; active rheumatic myocarditis; syphilitic aortitis; general passive congestion; acute pulmonary infarction, and nephrosclerosis.

This case was one of healed rheumatic lesion of the mitral valve, active rheumatic myocarditis and active syphilitic aortitis not involving the valve. It was an instance of rheumatic carditis with constitutional syphilis.

Case 6.—C. B., a Negro, 26 years old, was admitted to the City Hospital on Aug. 26, 1930, complaining of abdominal distention and pain. He had always been subject to sore throat; a history of syphilis and rheumatic fever was denied. For two years he had episodes of cough, palpitation, weakness and precordial pain, increasing in frequency and severity, followed by dyspnea and swelling of the abdomen.

Physical examination revealed the patient to be dyspneic and acutely ill. The pupils were normal. The entire precordium had a wavy impulse. There were double murmurs at the mitral and aortic areas. A diastolic apical thrill was present. The blood pressure was 130 systolic and 45 diastolic. The liver was three finger-

breadths below the costal margin. The urine had a specific gravity of 1.020 and showed no albumin or casts. He had many attacks of severe pain in the chest, sometimes accompanied by bloody expectoration. The pain was sometimes pre-

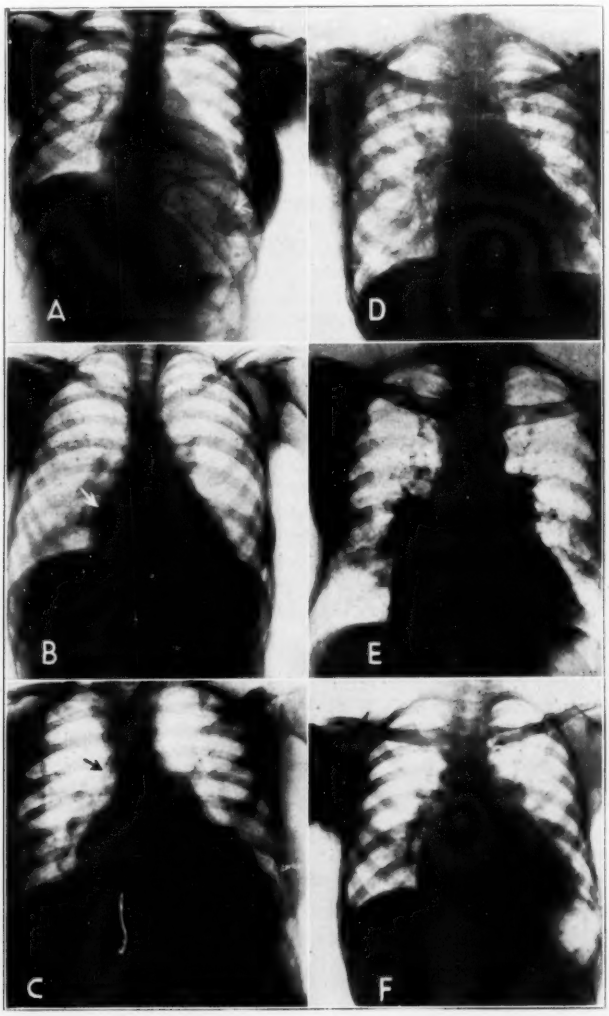

Fig. 8.—*A* (case 1), mitral and aortic insufficiency; *B* (case 2), appearance of the left auricle as a double shadow on the right side; *C* (case 2), shadow of the vena cava to the right of the aorta; *D* (case 3), marked pulmonary fibrosis; *E* (case 5), normal aortic and tricuspid valves, with accentuation of the ascending aortic curve; *F* (case 6), widening of the base of the aorta.

cordial only, and occasionally was elicited by pressure over the precordium; usually the pain was spontaneous. Urinary observations varied from no albumin to a heavy trace and from no casts to many, with abundant red cells. The patient's mental attitude was one of apprehension, and he was frequently extremely depressed. On October 1, he had an attack of severe precordial pain, became very weak and had a bloody expectoration. He apparently improved for a short time, and then died suddenly the same day. The temperature consistently ranged from 98 to 100 F. The pulse rate was always rapid, and consistently remained above the temperature level.

Roentgen examination revealed great enlargement of the left ventricle, with some widening of the base of the aorta. The other chambers of the heart were

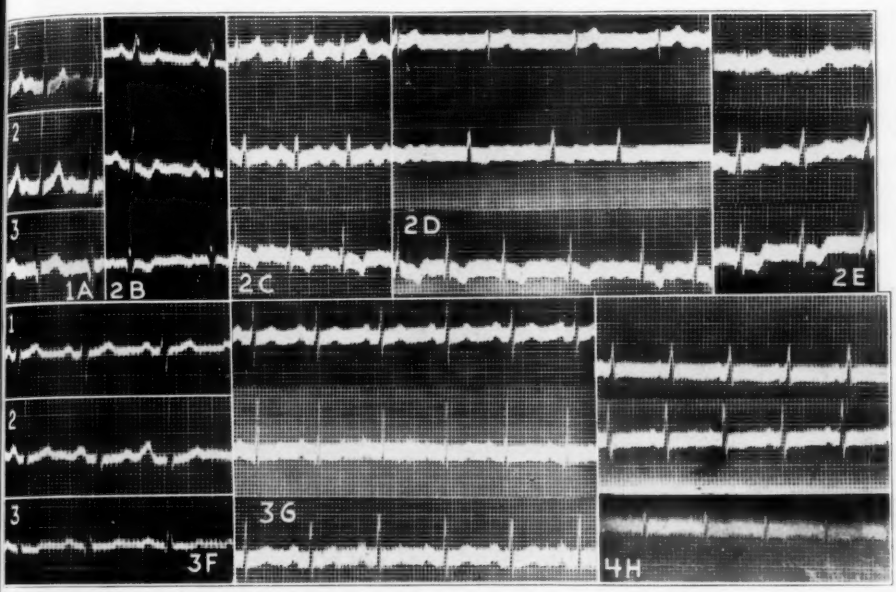

Fig. 9.—Electrocardiogram, showing: *1A*, neither left nor right axis deviation, mitral insufficiency, aortic stenosis and insufficiency, in an inspiratory type of heart; *2B, C, D, E*, auricular fibrillation following treatment with digitalis, with a constantly inverted T wave in lead 3; *3F*, slight Q wave in lead 3 and a diphasic T wave in lead 3; *3G*, no Q wave in lead 3, but an upright T wave; *4H*, a low voltage T wave.

enlarged. The definite widening of the base of the aorta and the type of heart showing aortic insufficiency, with the clinical findings, seemed evidence of the involvement of syphilis of the aortic valve.

The electrocardiographic study showed: normal sinus rhythm, with a top normal auriculoventricular conduction time (0.2 second); slurring and notching of the Q R S complexes, and the development of an inverted T wave in leads 2 and 3.

The clinical diagnosis was syphilitic aortitis, with aortic insufficiency; rheumatic heart disease; mitral stenosis and insufficiency, and coronary disease. The anatomic diagnosis was: chronic rheumatic endocarditis; chronic mural endocarditis; acute interstitial myocarditis; syphilitic aortitis involving the aortic valve; recent pulmonary infarctions; acute lobar pneumonia, and acute fibrinous peritonitis.

This case was one of rheumatic heart disease in which the rheumatic lesions were predominantly inflammatory, and the syphilitic involvement of the aortic valve profound. Superimposed was an acute generalized infection.

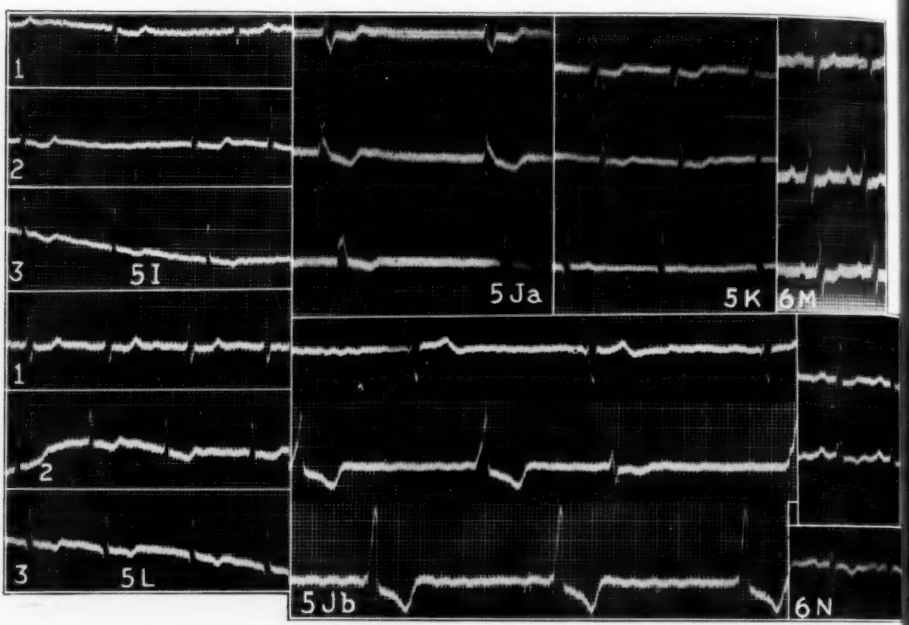

Fig. 10.—Electrocardiograms, showing: *5I*, auricular fibrillation; *5Ja*, usual leads; *5K*, direct chest leads with complete auriculoventricular dissociation, bundle branch block following digitalis and one returning cycle of usual rhythm; *5L*, return to the usual rhythm with the Q wave not present in *5I*; *6M*, diphasic T wave in leads 2 and 3; *6N*, inverted T wave in leads 2 and 3 and marked notching in lead 2 of the Q R S complex.

PATHOLOGIC ANATOMY

The criteria used for the diagnosis of rheumatic heart disease were: valvular involvement by a productive and inflammatory lesion tending to affect the mitral, aortic, tricuspid and pulmonic valves, and in that sequence; active pericarditis, and the presence of Aschoff bodies. For the diagnosis of syphilis the criteria used were: widening of the com-

missures; endarteritis of the vasa vasorum; narrowing of the mouths of the coronary arteries, and a pigskin-like appearance of the intima of the aorta. Great stress was placed on the gross and microscopic appearance of the commissures. The separation of the attachments of the cusps, the thickening of the leaflets, the pearly appearance of the intima and the endarteritis of the vasa vasorum with perivascular infiltration by lymphatic and plasma cells were considered characteristic of syphilis. These lesions have also been stressed by Saphir and Scott [6] and by Martland.[7] In control series of (1) rheumatic hearts and (2) hearts of syphilitic patients this commissural lesion was not found in the first group and almost invariably in the second. Spirochetes were not found in any case by the Jahnel and Warthin-Starry methods. The pathologic processes are summarized in table 1.

Hypertrophy was a feature common to all cases of the present group. The greatest weight occurred in the youngest patient (case 1), who had pancarditis. In the other extremely large heart (case 5), the absence of either active adhesive pericarditis or a valvular aortic lesion suggested the possibility of preexisting hypertension; histologic study of the kidney revealed benign nephrosclerosis.

The lesions due to rheumatic infection were marked in all six cases. There was adhesive pericarditis in two cases. Valvulitis was present in all. The mitral valve was involved in the entire series, the aorta in four cases, the tricuspid valve in four and the pulmonic valve in three. Myocardial Aschoff bodies were present in all but one case. Definite lesions of syphilis were limited to the aortic commissures in five instances; it was the predominant lesion in only one case. In two cases there was an intensely acute interstitial myocarditis, suggesting a terminal infection.

Stenosis of the mouths of the coronary arteries, so common in syphilis, was present in only half of the cases; these cases also showed the most marked widening of the commissures. Marked atherosclerosis of the main coronary arteries was present in three cases, in one instance with an active perivascular reaction. The patient in this case had clinical and classic attacks of paroxysmal dyspnea. Focal sclerosis was found in the patient with the renal changes of benign nephrosclerosis. This patient also had attacks of paroxysmal dyspnea and cardiac pain.

CLINICAL FEATURES

Race, Sex and Age.—Five of the patients were colored; three were men and two women. The only white patient was a man. The ages

6. Saphir, C., and Scott, R. W.: Involvement of the Aortic Valve in Syphilitic Aortitis, Am. J. Path. **3**:527, 1927.

7. Martland, H. S.: Syphilis of Aorta and Heart, Am. Heart J. **6**:1, 1930.

TABLE 1.—*Pathologic Processes in Hearts of Six Patients with Syphilitic and Rheumatic Infection*

Case	Weight, Gm.	Pericardium	Valves				Commissure	Myocardium	Endocardium	Coronary Arteries		Intrinsic Sclerosis
			Mitral	Aortic	Tricuspid	Pulmonic				Mouth	Main	
1	1,050	Adherent; rheumatic	Active rheumatic lesion; incompetent	Active mixed	Active rheumatic; stenosis	Rheumatic (microscopic); Aschoff bodies	Grossly normal; endarteritis of vasa vasorum	Gross apical scar; perivascular scar; acute interstitial myocarditis	Mural thromboses of left auricle; microscopic evidence of mixed cells	Normal	Moderate atheroma	In old scars
2	500	Nonspecific; visceral	Active rheumatic lesion; calcified; stenotic	Active rheumatic lesion; calcified; stenosis	Active rheumatic lesion; stenosis	Young vegetations	Slight widening; endarteritis	Perivascular scar; miliary scar; Aschoff bodies	Mural thromboses of left auricle	Normal	Moderate atheroma	Normal
3	600	Normal	Healed stenotic	Active rheumatic lesion; stenosis	Active rheumatic lesion; stenosis	Normal	Marked widening; endarteritis	Same as 2	Mixed cell foci (microscopic)	Stenosis	Moderate atheroma	Diffuse sclerosis
4	650	Adherent; rheumatic	Active rheumatic lesion; stenotic	Young lesions; competent	Normal	Rheumatic (microscopic)	Moderate widening; endarteritis	Same as 2	Same as 3	Stenosis	Atherofibrosis; marked perivascular inflammation	Sclerosis in scars
5	800	Nonspecific; visceral	Healed stenotic	Normal	Normal	Normal	Normal; syphilitic aortitis above valve	Perivascular scar; focal and diffuse Aschoff bodies	Dense foci of lymphocytes	Normal	Intense sclerosis	Focal sclerosis
6	500	Nonspecific; visceral	Active rheumatic lesion; incompetent	Syphilitic and rheumatic incompetent	Early vegetations	Normal	Marked widening; endarteritis	Perivascular scar; Aschoff bodies; acute interstitial myocarditis	Small fibrotic nodules	Marked stenosis	Marked atheroma	Normal

varied from the second to the fifth decades, 16, 26, 25, 34, 27 and 44 years.

Order of Appearance of Infections.—Rheumatic fever definitely preceded the syphilis in one case, and probably preceded it in another. The chancre appeared one year previous to the first attack of rheumatic fever in two instances. A history of rheumatic fever or of syphilis could not be elicited in two cases. The onset of a first attack of rheumatic fever relatively late in life following syphilitic infection was an interesting feature. Two hypotheses may be advanced to explain this phenomenon: 1. The syphilitic lesion rendered easier the secondary invasion by the rheumatic agent. Warthin [8] believed that latent syphilis in a young person predisposes him to secondary bacterial endocarditis. Coombs [9] likewise was of the opinion that the syphilitic valve is disposed to secondary invasion. Secondary invasion of the syphilitic valve resulting in the productive and inflammatory changes characteristic of rheumatic infection is, in our experience, uncommon. As suggested by Griggs,[10] the syphilitic process, by the very nature of endarteritis, automatically closes by the normal course of its evolution the portals of entry to secondary invaders. 2. The syphilitic process may cause an exacerbation of sufficient intensity of a low grade asymptomatic rheumatic disease to result in its passage over the threshold of clinical manifestation. The view generally held that the primary infection of rheumatic disease is acquired in the early years of life lends support to the second hypothesis.

In the four cases with sufficient data, the interval of time between the second infection, as based on the appearance of clinical symptoms, whether of syphilis or rheumatic fever, and the onset of the first appearance of cardiac decompensation was usually short, from three months to two years. In one case, mild decompensation occurred shortly before the syphilitic infection, to be followed in six months by a severe break. This is in contrast to the usual clinical course of uncomplicated rheumatic heart disease, and parallels the two cases mentioned. Only once was there a long interval, nine years. The patient acquired syphilis at the age of 33, a much later age than the others; rheumatic fever occurred at 34. The cardiac break, although delayed, occurred at a shorter interval than is usual in uncomplicated syphilis.

Course.—The clinical course of the disease was rapidly progressive after the first break in compensation, regardless of therapy. With one

8. Warthin, A. S.: Lesions of Latent Syphilis, Brit. M. J. **2**:236 (Aug. 10) 1929.

9. Coombs, C. F.: Syphilis of Heart and Great Vessels, Lancet **2**:236, 1930.

10. Griggs, LeRoy H.: Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect, Am. J. M. Sc. **164**:275, 1922.

exception it terminated within two years, and usually within one. One patient lived for ten months, two for one year, one for one and a half years and one for two years. In only one instance was there a long duration, seven years. The patient had frequent, easily precipitated cardiac breaks, and never attained well established compensation. The serious clinical course corresponds closely to the observations of Fordyce. In his series, the patients were reacting poorly to the rheumatic disease, and improved only when antisyphilitic therapy was instituted. In the present series, antisyphilitic therapy was much less efficacious, whether used intensively or conservatively. The explanation of the difference in the results possibly depends on the manifestations of syphilis: in the congenital form, aortic involvement is rare; in the acquired form, very common. Two factors, both tending to attack the cardiovascular system, are active in the present series. As pointed out by Pearse,[11] in experimental vaccinia and syphilis in the rabbit, the presence of concomitant active infections in the same animal may intensify the manifestations of each. The expectancy of life in our series of combined syphilis and rheumatic infection of the heart and great vessels resembled that of syphilitic persons of older years, with aortic insufficiency and congestive failure.

The direct cause of death was usually congestive failure. Two patients died suddenly; one, with a regurgitant lesion, had an extremely active inflammatory lesion and terminal suppurative myocarditis of undetermined etiology and the other died of diffuse sclerosis of the intrinsic coronary arteries. Intercurrent pneumonia terminated another case of mild decompensation. Table 2 gives in brief the essential features of the time element.

Pain.—Pain is one of the earliest symptoms of cardiac dysfunction, and may be difficult to interpret. It may vary from simple fatigue bordering on the threshold of pain to the anginal syndrome with the classic radiation. Certain rather definite clinical pictures are present with the various types of pain. In the anginal syndrome the pain may vary from a sense of constriction only, as described by White,[12] to the agonizing pain with the segmental distribution of Head[13] and Mackenzie.[14] For purposes of description this may be called the small vessel type of pain, and may be dependent on disease of the coronary

11. Pearse, L.: Reciprocal Effects of Concomitant Infections, J. Exper. Med. **47**:611, 1928.

12. White, P. D.: Medical Treatment of Angina Pectoris, Ann. Int. Med. **7**: 218 (Aug.) 1933.

13. Head, H.: Studies in Neurology, New York, Oxford University Press, 1920.

14. Mackenzie, J.: Angina Pectoris, New York, Oxford University Press, 1923.

arteries, particularly of the smaller radicles of the coronary circulation, the intrinsic myocardial vessels. Another type of anginal pain is limited to the precordium, and has possibly the same basic pathologic process. The aortic type of pain may be described as the large vessel type of pain, and is possibly due to increased intravascular tension associated with inflammatory disease of the wall of the vessels. It is frequently substernal and localized. In syphilitic aortitis the pain tends to be boring, substernal and localized. At times it is nocturnal, when it is possibly due to circulatory changes of the cardiorespiratory phenomena during sleep, which are of chemical and mechanical origin. Intravascular changes of pressure are probably basic factors. In aneurysms,

TABLE 2.—*The Time Element in Syphilitic and Rheumatic Infection*

Case	Relationship of Syphilis and Rheumatic Fever	Free Period Between Second Infection and First Cardiac Break	Age at Onset of Congestive Failure, Years	Duration of Course	Cause of Death
1.....	Rheumatic fever plus syphilis	Preceded syphilis; second break in 6 months	15	1½ yrs.	Congestive failure
2.....	Rheumatic fever (?) plus syphilis	3 months	25	10 mos.	Congestive failure
4.....	Syphilis plus rheumatic fever	2 years	27	7 yrs.	Congestive failure with sudden death
4.....	?	?	36	1 yr.	Lobar pneumonia
5.....	Syphilis plus rheumatic fever	9 years	43	1 yr.	Congestive failure
6.....	?	?	24	2 yrs.	Congestive failure with sudden death

there is an added factor of pressure on surrounding structures. Occasionally, aneurysm is associated with axillary pain, probably due to extension of the syphilitic process to the aortic branches. Clinical observation of a patient of McCarthy [15] in arteriovenous anastomosis for the relief of aortic aneurysm demonstrated a shift of the pain from right to left, the opposite side, owing to the change of intra-aortic pressure subsequent to the operative procedure. In aortic arteriosclerosis the pain is much milder than in syphilis, but has the same distribution.

The type of pain accompanying rheumatic infection is of a different character. It is recurrent, probing and usually limited to the pre-

15. McCarthy, P. A.: Treatment of Aneurysms of the Thoracic Aorta and Innominate Artery by Distal Arterio-Venous Anastomosis, Ann. Surg. **91**:161, 1930.

cordium, and does not tend to radiate. Frequently it is limited to the region of the apex. It is intensified by pressure over the region. During periods of exacerbation of the rheumatic infection it is more prominent. Rheumatic hearts with advanced mitral disease sometimes have the true anginal syndrome, possibly due to combined coronary disease, inflammation of the large vessels and pressure phenomena, as of a large left auricle.[5] Sweeny's[16] patient with mitral stenosis was relieved only by morphine and cervical sympathectomy. Rarely, the patient experiences pain over the pulmonary artery; this region is not tender to pressure, but the pulmonic area on fluoroscopic examination appears dilated. Possibly the clinical observation rests on the presence of an inflammatory lesion of the region, with increased intravascular tension. Arthritic pains, pain in the vessels due to thromboses, pain in the lungs and splenic pain resulting from thromboses of the organs accompany rheumatic infection in heart disease. The pain accompanying rheumatic heart disease may be compared to that elicited over any area of inflammation, and may be described as an infectious type of pain.

In the present series, pain was present in five cases. In three it was a prominent feature. In only one case was there pain in the joints. It was of the infectious type in two other cases, both with extremely active lesions, one with multiple thromboses. It was of the precordial anginal type in another case, which developed during the course of the illness and dominated the picture during the last few months. This patient also had attacks of paroxysmal dyspnea. Histologic study later revealed generalized sclerosis of the intrinsic coronary arteries. Another patient had cardiac pain with attacks of dyspnea in which the pain disappeared with progressive congestive failure.

The only patient with aortic regurgitation predominantly syphilitic had the aortic type of pain in the chest accompanied by bloody expectoration. He did not have axillary pain, which sometimes accompanies disease of the aorta and its branches; he had the coronary type of pain and also abdominal pain.

Dyspnea.—Dyspnea in cardiac disease is usually of the congestive failure type; at times it is paroxysmal. Paroxysmal dyspnea associated with edema of the lungs, with or without cardiac pain, is to be differentiated from dyspnea of cerebral origin with the Biot type of respiration. Mackenzie[17] believed that the paroxysmal type associated with heart disease was due to a lessened cardiac output. Pratt[18] said that this

16. Sweeny, John A.: Personal communication to the authors.

17. Mackenzie, J.: Cardiac Asthma, Brit. M. J. **2**:1231, 1911.

18. Pratt, J. H.: Cardiac Asthma, J. A. M. A. **87**:809 (Sept. 11) 1926.

type of dyspnea is never accompanied by failure on the right side, but originates in the left ventricle. It is usually not associated with valvulitis, but shows a tendency to develop anginal pain. Weiss [19] believes that one important factor is increased blood load in the lungs due to change in the position of the body and the presence of disease of the lungs.

In the present series, five patients had the progressive type of congestive failure; one of them had paroxysmal dyspnea for a time. In the remaining case the congestive type of dyspnea was present at the onset of symptoms, but was later replaced by a paroxysmal type which dominated the clinical course during the last year. Histologic study revealed diffuse sclerosis of the intrinsic coronary vessels. We believe that disease of the smaller radicles of the intrinsic coronary system in the final distribution to the muscle fibers results in a lessened margin of physiologic function, and could be one of the basic factors in the pathologic physiology of the paroxysmal type of breathing.

Heart Sounds.—Changes in the normal heart sounds are due to associated pathologic processes. The tendency in rheumatic valvulitis, as seen at autopsy, is toward healing with fibrosis and calcification leading to definite rigidity of the structure and a stenotic lesion. It is only in the rapidly progressive lesion in which the inflammatory element predominates over the tendency to heal that the lesion is essentially regurgitant. This applies to all the valves involved. On the other hand, in syphilis limited to the aortic system, there is definite retraction of the valve cusps, with shortening of the leaflets, smooth thickening and rolling back of the edges of the valve and a widening of the ring, due to commissural disease, a lesion resulting primarily in insufficiency. The valves are usually much softer and more leathery than the lesion resulting from rheumatic disease, and calcification, when present, is a much finer deposit and is well masked by the fibrosis.

The differential diagnosis of an aortic lesion rests largely between the rôle of rheumatic fever and that of syphilis. Sclerosis, with its varied etiology, must also be considered. Because of the predominance of stenosis in rheumatic aortic disease, the heart sounds are rougher and higher pitched, and there is a sharper differentiation between the systolic and the diastolic phase of the murmur. There is often a faint first sound that is muscular in quality, almost masked by the systolic murmur, an almost imperceptible midsystolic-diastolic pause and the diastolic murmur. In syphilis, on the other hand, the rolled back,

19. Weiss, Soma, and Robb, G. P.: Cardiac Asthma (Paroxysmal Dyspnea) and the Syndrome of Left Ventricular Failure, J. A. M. A. **100**:1841 (June 10) 1933.

smooth edges give a soft blowing, low-pitched systolic murmur followed immediately by a low-pitched decrescendo murmur; the systolic phase is scarcely separated from the diastolic phase, making the "lub-tu" murmur characteristic of the aorta and aortic valves. Rarely, a deformed valve behaves like a vibrating reed in the blood stream, producing a high-pitched musical murmur approaching a sound which can be heard in the brachial and radial arteries, a mechanism produced only by the smooth fibrotic lesion of syphilis.

In the present series, in five of the six cases, there were harsh mitral stenotic murmurs with diastolic murmurs and an accompanying precordial thrill. In one case there was only a systolic murmur at the mitral valve, and in one a blowing systolic murmur at the aortic area. In another case there was a systolic murmur transmitted to the carotid arteries with a thrill over the vessels and a diastolic murmur; postmortem examination revealed a rheumatic lesion of the aorta. The one case of aortic regurgitation diagnosed clinically as frank aortic regurgitation, syphilitic in origin, had no detectable first sound, but a loud blowing diastolic murmur transmitted down the border of the sternum. This man had markedly widened commissures and smooth rolled back cusps of the valves with thickened free valve flaps. The histologic examination revealed evidence of a marked syphilitic and an extremely active rheumatic lesion. The lesion was predominantly inflammatory, and definite conclusions as to the predominant etiologic factor could not be made.

Three patients of this series had a typical rheumatic fever of the subacute type, low grade, with periods of exacerbations. A low grade elevation of temperature usually in the neighborhood of 99 F. was present in two others. In only one case was the temperature normal until the onset of lobar pneumonia; the rheumatic disease, although active in the pathologic sense, was not of sufficient intensity to produce the rise in temperature ordinarily associated with this, a subclinical infection.

Eyegrounds.—Stokes [20] called attention to a symptomatology which is apparently rheumatic, but which on careful observation is that of syphilis in disguise. Rarely it may be difficult to determine the etiology of aortic valvular disease. The eyegrounds and reflexes may give valuable information as to the presence of neurosyphilis. One patient of this series had slightly irregular pupils, with a sluggish reaction to light and in accommodation. Of the remainder, two showed sclerotic vessels. Only one, therefore, had changes suggestive of syphilis.

20. Stokes, J.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926.

Serology.—The Wassermann reactions of the blood in the entire series were consistently positive. In one case of secondary syphilis, the reaction became negative under therapy. We feel that repeatedly positive reactions are definite evidence of syphilitic infection, and that any case of rheumatic cardiac disease showing such results should be carefully studied to evaluate the rôle of syphilis as an added load.

Roentgenology.—Based on six years' study of cases of syphilitic and rheumatic cardiac disease checked by autopsy, the following criteria were used in the differential diagnosis of syphilitic and rheumatic heart disease: (1) for rheumatic infection of the valves, (*a*) predominant enlargement of the left auricle, (*b*) early pulmonary stasis and widening of the pulmonary vessels, (*c*) enlargement of the right ventricle and (*d*) normal width of the aortic ring; (2) for syphilitic aortitis involving the aortic ring, (*a*) widening of the aortic ring (syphilis not involving the ring does not cause such widening), (*b*) enlargement of the left ventricle, (*c*) late engorgement of the pulmonary field after the onset of congestive failure and (*d*) late enlargement of the right ventricle dependent on right-sided failure and strain.

In our series, four patients revealed typical stenotic lesions of the mitral and aortic valves. In two, widening of the aortic ring developed under observation. One case remained of the regurgitant type; the pathologic process was strikingly inflammatory, with slight evidence of a tendency to heal. The remaining case presented several findings which offered difficulty in interpretation. Although the left auricle was enlarged to the degree compatible with a stenotic mitral orifice, the left ventricle was correspondingly disproportionately large. In the presence of an aortic ring of normal width and a prominent supraventricular aortic curve, the possibility of hypertension suggested itself. Renal histologic study revealed benign nephrosclerosis.

Five patients had the inspiratory type of heart seen in mitral stenosis; in the last case, that of aortic regurgitation, the heart was of the expiratory type.[21] Table 3 summarizes the roentgen ray observations.

Electrocardiographic Study.—The electrocardiographic records parallel certain changes in the normal functions of the heart due to disease and may give valuable information as to anatomic lesions, rate and rhythm. They do not determine the etiology, but may give confirmatory evidence of clinical diagnoses. Friedlander [22] found that electrocardiographic records were not pathognomonic of rheumatism, syphilis or

21. Chandlee, G. J., and Burville-Holmes, E.: Clinical and Roentgen Findings in the Study of the Heart and the Great Vessels, Am. J. M. Sc. **178**:304, 1929.

22. Friedlander, A.: The Electrocardiogram in Luetic, Arteriosclerotic and Rheumatic Heart Disease, Am. Heart J. **5**:15, 1929.

TABLE 3.—*Summary of Roentgenographic Observations*

Case	Left Ventricle	Left Auricle	Right Ventricle	Right Auricle	Aorta	Pulmonary Artery	Measurements				Type of Heart
							Left Branch, Cm.	Right Branch, Cm.	Base, Cm.	Chest at Ninth Rib, Cm.	
1	Marked enlargement	Marked enlargement, showing as double shadow on right side	Marked enlargement	Moderate enlargement	No sclerosis; no widening of base	Main branches not widened; arc accentuated	10.3	4.1	4.0	24.5	Inspiratory
2	Enlarged	Similar to case 1	Enlarged	Moderate enlargement	No sclerosis; no widening of base	Main branches widened; marked enlargement of conus; shadow of cava to right of aorta	14.4	6.2	Cannot be measured	31.0	Inspiratory
3	Enlarged	Enlarged	Enlarged	Moderate enlargement	Widened; no widening of base	Main branches widened; marked signs of pulmonary fibrosis	11.8	4.4	5.5	27.0	Inspiratory
4	Moderate enlargement	Enlarged	Enlarged	Moderate enlargement	Slight sclerosis	Passive engorgement	9.3	5.8	7.2 (2d rib)	23.7	Inspiratory
5	Marked enlargement	Enlarged	Enlarged	Enlargement	Accentuated; ascending aortic curve	Main branches widened	Not available				Inspiratory
6	Greatest enlargement	Enlarged	Enlarged	Enlargement	Moderate widening; base widened	Main branches widened	11.0	5.2	5.5	26.5	Expiratory

arterial sclerosis in heart disease, but that the electrocardiograms in syphilis and arteriosclerosis showed a striking parallelism.

The most striking feature in the electrocardiographic study in this series was the occurrence of auricular fibrillation in the cases showing the most extensive auricular disease. In one case auricular fibrillation developed under doses of digitalis considered within therapeutic limits, and promptly returned to normal rhythm after the administration of digitalis was discontinued. In the other case, with established auricular fibrillation, complete heart block with bundle branch block and a Q wave in lead 3 developed on treatment with digitalis and returned to auricular fibrillation after the drug was withdrawn. The direct chest leads showed one returning cycle of the dominant rhythm in this case. These observations suggest that active cardiac infection and disease render the heart more susceptible to the toxic effects of digitalis.

A rate of 100 or over was present at some time in five of the six cases. All but one (chronic auricular fibrillation) had an auriculoventricular conduction time of 0.2 second (top normal). Prolonged auriculoventricular conduction time is recognized as a frequent finding in rheumatic heart disease. The anatomic explanation possibly lies in an inflammatory lesion of the auricular wall extending upward from the mitral valve in the neighborhood of the portion of the conduction system lying between the auriculoventricular node and the bundle of His. The extent of the lesion in the auricular wall may likewise determine the liability to the development of auricular fibrillation.

Slurring was the most constant change in the Q R S complex, being present in five of the six cases, and was evidence of myocardial disease. In one case there was marked notching in leads 2 and 3. A large Q wave appeared in lead 3 in one instance after auriculoventricular dissociation, and remained constant but of less amplitude on return to the dominant rhythm of auricular fibrillation. In another case a Q wave appeared, but subsequently disappeared; digitalis was not administered in this case.

A diphasic T wave was the change most commonly present. T waves were also found to be influenced by digitalis. The one exception was the case in which the T wave in lead 3 was always inverted. The T wave became more evident as the disease progressed. This was the case of marked progressive cardiac enlargement, with increasing right axis deviation and right ventricular hypertrophy. In one case, with marked notching of the Q R S complex, a definite T wave found in coronary disease with a low take-off of the S T interval developed. Juster and Pardee [23] found this abnormality in patients with aortitis.

23. Juster, I. R., and Pardee, H. E. B.: Abnormal Electrocardiograms in Patients with Syphilitic Aortitis, Am. Heart J. **5**:84, 1929.

This case was of the regurgitant type, with an active syphilitic aortic valvular lesion and extreme stenosis of the mouths of the coronary arteries.

TABLE 4.—*Summary of Electrocardiographic Observations*

Case	Date	Rhythm*	Rate	A. V. Conduction	Q R S	S T	Axis Deviation	Digitalis
1A	6/ 1/27	NS*	115	0.22	Slurring in leads 1, 2, 3	Upright T1-2-3	None	None
2B	1/31/27	NS	75	0.20	Slurring in leads 1, 2, 3	T1, T2 diphasic; T3 inverted	None	10 cc. 1/26 to 1/31/28
C	4/ 5/28	NS	107	0.16-0.20	Slurring in leads 1, 2, 3	T1, T2 upright T3 inverted	Slight right	24 cc. 2/1 to 3/26/28
D	5/ 8/28	AF†	80	....	Slurring in leads 1, 2, 3	T1 upright; T2 diphasic; T3 inverted	Right	74 cc. 4/10 to 5/8/28
E	6/21/28	NS	107	0.16-0.20	Slurring in leads 1, 2, 3	T1 upright; T2 diphasic; T3 inverted	Slight right	4 cc. 5/16 to 6/7/28
3F	5/17/28	NS	90	0.20	Slight Q wave in lead 3	T3 diphasic	None	None
G	8/28/28	NS	88	0.20	Q wave absent in lead 3	T2 diphasic; T3 upright	Slight right	None
4H	1/ 9/28	NS	110	0.20	Slurring in leads 1, 2, 3	Low voltage	None	38 cc. 12/27/27 to 1/3/28, before admission
5I	4/ 9/29	CAF‡	60	....	Slight slurring in leads 1, 2, 3	T1, T2, T3 diphasic	Tendency to right	None
Ja	6/11/29	CAF; A. V. dissoc.§	40	....	Notching, slurring, widening in leads 1, 2, 3	T1 diphasic; T2, T3 inverted	Right	34 cc. 5/31 to 6/11/29
Jb	6/13/29	CAF; A. V. dissoc.	40	....	Notching, slurring widening	.....	.....	Same as Ja
K	6/20/29	CAF	60	....	Slurring in leads 1, 2, 3; Q wave in lead 3	T1, T2 diphasic; T3 slightly inverted	None	None
L	8/26/29	CAF	80	....	Slurring in leads 1, 2, 3; Q wave smaller in lead 3	T1, T2 diphasic; T3 inverted	Slight right	12 cc. 7/10 to 7/15/29; 17 cc. 8/10 to 8/26/29
6M	8/19/30	NS	88	0.20	Slurring, slight notching in leads 1, 2, 3	ST comes off slightly below iso-electric level; T1 upright; T2, T3 diphasic	None	None
N	9/ 6/30	NS	100	0.20	Slurring in lead 1; widening in leads 2, 3	ST comes off slightly below iso-electric level; T2, T3 coronary	Left	18 cc. 8/9 to 9/6/30

* Normal sinus rhythm.
† Auricular fibrillation.
‡ Chronic auricular fibrillation.
§ Auriculoventricular dissociation.

Axis deviation, when present, usually tended to the right. The inspiratory type of heart was present in all these cases, as shown by roentgenographic study, and the majority presented tricuspid lesions. The only case of predominant regurgitant aortic insufficiency with the expiratory type of heart showed roentgenographically the development of an axis deviation to the left. The electrocardiographic observations are summarized in table 4.

SUMMARY

The study of the clinical course and pathologic changes in this series of six cases of combined syphilitic and rheumatic infection revealed that the predominant lesion was rheumatic. A stenotic lesion of the mitral valve occurred in four of the six cases. The remaining two cases had predominant insufficiency of the mitral valve from an extremely active inflammatory lesion. In five cases active rheumatic valvulitis involved the aorta, three times with stenosis and once with an incompetent valve. The incompetent valve had an extremely active rheumatic and an active syphilitic infection. In one case the aortic valve was normal; syphilitic aortitis was present above the valve, but it did not involve the ring. The evidence of syphilis was most pronounced in the commissural region and frequently limited to it. Syphilis of the myocardium could not be proved. Associated coronary disease of the small vessels complicated one case. One case showed aortitis involving the mouths of the coronary orifices.

The combined infection apparently occurs most frequently in the colored race, five of the six patients being Negroes, and it is likely to manifest itself during young adult life. The histories suggested that the rheumatic infection preceded the syphilis, and was reactivated by it. The clinical course was rapidly progressive and usually typically rheumatic. One case of coronary sclerosis had the clinical course of coronary disease and not syphilis or rheumatic fever.

Pain was present in five of the six cases and was usually of the rheumatic infectious type. Dyspnea was usually of the congestive failure type. Paroxysmal dyspnea occurred in the case with coronary sclerosis. The heart sounds in rheumatic stenotic lesions tend to be rough and high-pitched. In the aortic region, even when complicated by regurgitation, the rough, high-pitched sounds seemed evidence of stenosis. In syphilis of the aortic valve with insufficiency, the heart sounds usually are lower pitched and softer, and the systolic-diastolic pause heard in stenosis of the valve is absent. The eyegrounds showed evidence of syphilis in one case. Two showed sclerotic changes, and the case in which the heart was never well compensated revealed marked engorgement of the veins. Serologic reactions were positive in all cases.

Roentgen examination revealed stenotic lesions of the mitral and aortic valves. Five of the hearts were of the inspiratory type; one with a predominant aortic lesion of regurgitation was of the expiratory type.

The most frequent findings in the electrocardiogram were tachycardia and from top normal to prolonged auriculoventricular conduction time. All but one case showed slurring of the Q R S complex. Three showed a tendency to right axis deviation, only one to left axis deviation.

Two cases with most marked auricular disease showed a conspicuous toxic reaction to digitalis.

CONCLUSIONS

1. The lesions and the clinical course in the six cases of combined syphilitic and rheumatic infection of the heart and great vessels were mainly rheumatic; in one case only was the rôle of syphilis of equal importance to that of rheumatic infection.

2. The combined active infections carry a much graver prognosis than either infection occurring separately.

3. Dyspnea of the coronary and congestive failure types must be clearly differentiated for the institution of correct therapeutic measures.

4. Heart sounds help in the differential diagnosis of rheumatic and syphilitic aortic disease.

5. Roentgenology is a valuable aid in the differential diagnosis between the rôles of syphilis and rheumatic infection in the production of cardiovascular pathologic processes.

6. The electrocardiogram is of most value in studying the clinical course of disease and as a check on digitalis therapy.

7. Study of the clinical characteristics of pain helps to differentiate more clearly the basic pathologic process associated with the various types of cardiovascular disease.

Dr. George Plehn made the roentgenographic studies of these cases. The observations are to be reported by him in greater detail in a separate communication.

SOME FACTORS DETERMINING THE VARIABILITY OF SKIN TEMPERATURE

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The application of the thermocouple has provided a new and exact technic for the determination of skin temperatures. The fineness of the instrument, however, has to a certain extent created a false impression as to the accuracy of the determinations. The inherent variability of the phenomena governing the level of the surface temperature has undergone little investigation, and its effect on the reliability of single determinations has been largely unchecked. In the present investigation an attempt was made to determine the magnitude of the variation to be expected in such a study.

METHOD

The investigation was conducted in a windowless, brick-lined, circular room, the temperature of which was maintained between 23 and 24 C. and the air flow of which was so regulated as to be imperceptible to the nude subject. The relative humidity was measured at frequent intervals by a sling psychrometer. The subjects were male schizophrenic patients with no organic disease. The fact that the subjects were psychotic presumably has no significant bearing on the question at issue. They were studied under basal conditions, completely unclothed and lying on a bed containing a mattress covered with a sheet. The thermocouple was of the type utilized in the investigations of Benedict, Koropatchinsky and Finn[1] and could be read accurately to within 0.05 C. (0.09 degree F.). The various points on the skin selected for measurement are designated by numbers, and their location can be identified on the figure in chart 1.

The first investigation was undertaken to determine the time at which the skin temperature attained an equilibrium with the conditions of the test room so that the rest period might be of sufficient length to nullify differences in the previous environment. For this purpose, six patients were studied under fasting conditions. After a fifteen minute rest and every fifteen minutes thereafter over a total period of one and one-half hours, readings were taken at each of the seventeen points designated in chart 1.

From the research service of the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research.

1. Benedict, F. G.; Koropatchinsky, and Finn, M. D.: Etude sur les mesures de température de la peau, J. de physiol. et de path. gén. **25**:1, 1928.

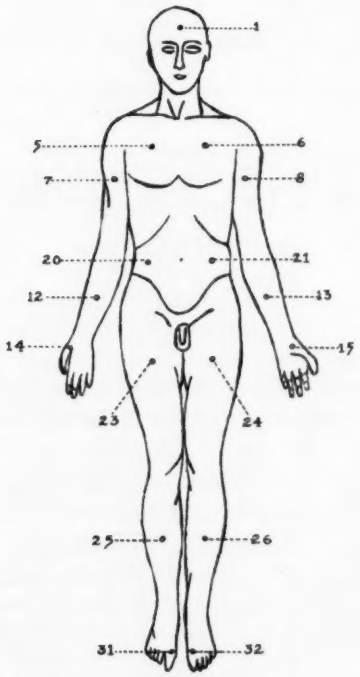

Chart 1.—Topographic location of points studied.

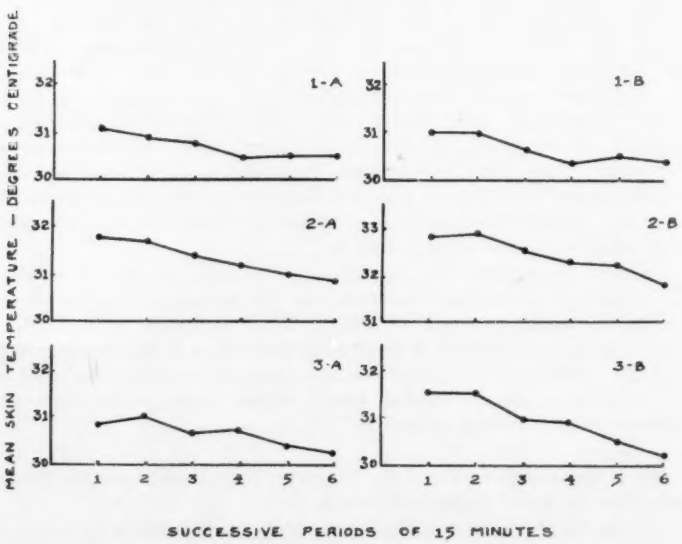

Chart 2.—Means of skin temperature for six patients taken every fifteen minutes during a one and one-half hour period.

RESULTS

The behavior of the subjects is illustrated in chart 2, in which is depicted the slope of the mean of the seventeen readings for each of the six patients. From the first reading there was a general fall in the temperature, which in four of the cases, at least, had not attained a resting level at the end of ninety minutes. Two of the patients had reached an apparent equilibrium at sixty minutes. It is evident, then, that in the majority of subjects a longer period than one and one-half hours is necessary to attain an equilibrium to environmental conditions such as were present in the test room. As there is an individual difference in the curves, a short rest period cannot be utilized in the supposition that the error in such a procedure would be a constant one.

Closer analysis of the figures reveals other features of interest. The subjects were studied in pairs, each two being subjected to the same

TABLE 1.—*Drop in Skin Temperature During a One and One-Half Hour Interval* *

Forehead (1)†	—0.17‡
Chest (5)	0.78
Abdomen (20)	0.98
Upper part of leg (23)	0.76
Upper part of arm (7)	1.22
Lower part of arm (12)	1.06
Lower part of leg (25)	0.
Thumb (14)	1.61
Toe (31)	—0.24‡

* Values are expressed in degrees Centigrade.
† In this and the following tables the figures in parentheses are those used to indicate the various points on the body in chart 1.
‡ The minus sign indicates a rise in temperature.

pretest and the test conditions. The dominating influence of environment on the skin temperature is shown by the fact that if the first readings for the two members of each pair are compared a strong positive relationship is found; furthermore, if the last readings are similarly matched, apparently an equally good correlation is evident. As the fifteen minute reading is representative of the pretest conditions and the ninety minute period more indicative of the test environment, the equalizing effect of external factors on the skin temperature is evident. The sensitivity of the responsive mechanism is further shown by the greatest resemblance between the slopes for the members of each pair than between those for different pairs. For this reason, it seems desirable in any comparison of skin temperatures in normal or pathologic conditions to measure one person from each group simultaneously, so that errors due to environmental differences may be equalized and thus reduced in importance.

Despite the general tendency toward a continuous fall in skin temperature on recumbency, the process was not manifested uniformly

over the entire body. In table 1 is a comparison of the total fall in temperature over the one and one-half hour period during which the various areas were studied. In general the change was of greater extent in the peripheral than in the central points. Over the forehead there was a slight rise in temperature. On the thumbs there was a fall of over 1.5 C. (2.7 F). The outstanding exception was in the case of the toes, in which a slight elevation of temperature occurred. This may possibly have been due to the fact that the temperature of the toes was so low (25 C. [73.4 F.]) that it could fall no further under the given environmental conditions. The more marked fluctuation in the extremities is in accordance with the greater rôle which they play in the adaptation of the surface temperature to environmental conditions.[2] As it is the extremities which are of most interest in clinical studies of skin temperature, the error involved in not permitting a proper period of adjustment undoubtedly may be a factor leading to erroneous conclusions.

A second phase of the investigation was the determination of the minute-to-minute variation in the temperature of the skin. In any extensive study of surface temperatures, many readings must be made extending over a varying length of time. At an environmental temperature of 23 C. the organism undergoes a continuous loss of heat with a consequent reflection in the temperature of the skin. Under such conditions any single reading is representative only of the state existing at the moment the reading was made, and it is consequently desirable, in making an exact study, to determine the amount of variation occurring over the period of the investigation.

Accordingly, for eight patients, after a rest period of thirty minutes, repeated measurements were made over five points (*1, 5, 12, 23* and *31* in chart 1) considered representative of various areas on the body. In the case of the first two patients the readings were made in each area at intervals of one minute over a period of five minutes. It was immediately evident, however, that a slight but consistent rise in temperature was present in the later readings. While the exact cause of this trend was uncertain, it was considered to be due to a reflex vasodilatation from the irritant effect of the slight pressure or to a blanketing effect of the ebony support of the thermocouple during its ten second period of application. To minimize the possible effect of this factor, the interval between measurements was increased to two minutes and the total period to ten minutes. Despite this, however, the increase in temperature was still evident on the forehead (*1*), chest (*5*) and toe (*31*), as shown in table 2, but not on the lower part of the arm (*12*) or the upper part

2. Maddock, W. G., and Coller, F. A.: The Rôle of the Extremities in the Dissipation of Heat, Am. J. Physiol. **106**:589 (Dec.) 1933.

of the leg (*23*). This upward trend is more important as the previous investigation has shown that a fall in skin temperature would be expected during this period.

The presence of this systematic tendency of the temperature to rise on repeated applications of the thermocouple somewhat complicates the analysis of the short time variation, but its evaluation may be aided by a study of the areas in which it did not occur. In table 3 are enumerated the standard deviations of the variation occurring over these portions of the body surface. On the lower part of the arm (*12*) and

TABLE 2.—*Means of Surface Temperature Measurements on Six Patients at Consecutive Two Minute Intervals* *

	First Minute	Third Minute	Fifth Minute	Seventh Minute	Ninth Minute
Forehead (1)	33.67	34.06	34.27	34.35	34.43
Chest (5)	32.60	32.72	32.87	32.95	32.99
Lower part of arm (12)	32.02	32.06	32.10	32.13	32.14
Upper part of leg (23)	32.18	32.12	32.11	32.11	32.09
Toe (31)	26.18	26.26	26.31	26.42	26.85

* Values are expressed in degrees Centigrade.

TABLE 3.—*Variation for Five Consecutive Readings at Two Minute Intervals in Six Patients* *

	Standard Deviation
Forehead (1)	0.364
Chest (5)	0.200
Lower part of arm (12)	0.100
Upper part of leg (23)	0.075
Toe (31)	0.440

* Values are expressed in degrees Centigrade.

the upper part of the leg (*23*), the variation over a ten minute period in the majority of instances was no greater than 0.1 C, (0.18 F.), and it is possible that were this disturbing upward trend eliminated the expected change over the entire skin would be approximately of this extent. Such a value, however, would imply a possible maximum variation of 0.5 C. (0.9 F.), an error of sensible proportions. In view of this fact, in an extensive investigation it might be well to vary among the subjects the order in which the different regions are measured so that there might be no weighting of the values of any particular area. In this way, the error arising under such conditions may be so distributed that its importance becomes negligible.

Another possible source of variation lies in the selection of the points at which the temperature is to be determined. In repeated studies on a single subject or in comparative studies on several subjects, a certain amount of error inevitably must be introduced in locating the points to

be investigated unless great care is taken to relate them to fixed anatomic landmarks. As this is extremely time-consuming, it was thought to be more practicable to determine the approximate variation existing within a small area surrounding a given point. Accordingly, in eight patients, the five points previously noted were marked, and around each one were selected four spots equidistant from each other and so placed as to be representative of a circle of a radius of ½ inch (1.27 cm.).

The investigation first disclosed that the systematic trend noted in the previous study was not evident, the variation of the peripheral from the central points being of an entirely random nature. In table 4 are summarized the constants of the distributions of the differences of the surrounding points from the central ones. The mean differences are small, but this is to be expected, because the variation is such as to result in a cancellation of the plus against the minus deviations. The

TABLE 4.—*Constants of Distributions of Differences of Adjacent Points from Central Points in Eight Patients* *

Point	Minimum	Maximum	Mean	Standard Deviation
Forehead (1)	−0.55	+0.30	−0.11	0.21
Chest (5)	−0.70	+0.25	−0.13	0.19
Lower part of arm (12)	−0.50	+1.10	+0.16	0.41
Upper part of leg (23)	−0.95	+0.50	−0.14	0.25
Toe (31)	−1.30	+0.05	−0.05	0.51

* Values are expressed in degrees Centigrade.

body points in general show greater consistency around them than do the peripheral ones; in the latter case there is more opportunity for anatomic variation within the small area investigated. In the majority of instances these differences extended from 0.2 C. (0.36 F.) to 0.5 C., depending on the topographic location. The maximum errors, however, may be much greater, being over 1 C. (1.8 F) on the toe, even in such a small series as the one studied. It is evident, therefore, that in any careful study of skin temperatures the utmost care should be taken to localize the desired point carefully, for a slight variation in placement may result in appreciable errors. It would perhaps be desirable to obtain several readings around a given point, the mean being taken as the typical value for that area, and in this way minimize the magnitude of the possible variation.

COMMENT

This brief study has revealed that the experimental errors in the determination of skin temperatures are somewhat larger than is ordinarily assumed. Differences in temperature of about 0.5 C. are to be examined critically before any significance can be attached to them. It seems superfluous to make measurements to the fineness of which

the thermocouple is capable when the physiologic variation is ten times that of the instrument. The most important finding presented in this study is the slowness with which the skin comes into equilibrium with environmental conditions. In order to eliminate completely the effects of the pretest environment, the skin must be exposed under uniform conditions for several hours before accurate readings can be made. This seems to be an ideal practically impossible of attainment in clinical practice, for it necessitates the possession of a chamber in which temperature, humidity and rate of air flow can be controlled. Nevertheless, unless such a standard procedure is maintained, gross differences alone can be accepted as reliable.

SUMMARY

In a study of the inherent variation of the skin temperature in persons with no organic disease, it was found that:

1. The skin does not adapt itself in the majority of cases to a given temperature for at least one and one-half hours, and for approximate equilibrium several hours are probably necessary.

2. The minute-to-minute variation in the skin temperature is usually of the nature of 0.1 C. over the entire body, but it may be as high as 0.5 C.

3. An error in the placement of the thermocouple of one-half inch from the desired point usually results in a change of from 0.2 to 0.5 C., but in the extremities the change may be as great as 1 C.

A TEST OF BLOOD FLOW TO AN EXTREMITY

ITS CLINICAL APPLICATIONS

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CHICAGO

The number of vascular tests is legion. Boerhaave is quoted as crediting Jan Swammerdam with the construction of the first plethysmograph. Stephen Hales, the English clergyman, was the first to measure blood pressure by cannulating the carotid artery of a horse in 1733. During the period that followed, accurate measurements of blood pressure in animals were made, while this study in man remained virtually a sealed book. Then, in 1896, Riva-Rocci introduced the armlet method, which gave reliable results and accurate estimations of systolic pressure. A cuff of standard width was introduced which eliminated error, and later a complete description by Kortoff of the auscultatory changes assured exact diastolic as well as systolic readings.[1] A few workers still favored the oscillatory determinations.

During the last ten years there has been renewed interest in the peripheral vascular diseases. New methods have been devised, and the problem has been approached afresh. Sensitive thermocouples were used by Lewis [2] to measure skin temperature, and the work of Brown,[3] Scott [4] and Simpson [5] in thrombo-angiitis obliterans must be mentioned. The thermocouple, admittedly accurate, is too liable to gross external error in its practical use. Changes in humidity, fluctuations of room temperature, wind currents, the amount of sweating and other factors

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which are exceedingly difficult to control often vitiate readings. This shortcoming led Johnson [6] and Scupham and Gilbert [7] to favor a finger plethysmograph. The most ingenious device of their own invention gives simple accurate records of the pulse wave of the finger or toe. It also serves to differentiate between spastic and obstructive vascular lesions. The improved Pachon oscillometer was used extensively in France by Cawadias,[8] and in America by Samuels,[9] Kramer [10] and Friedlander.[11]

A different approach was the study by Lewis [12] of changes in the color of the skin. He added a full page of colored illustrations to his report to serve as a guide or index. In addition, he studied exhaustively the flush and vascular reactions to histamine.[13] Later, de Takáts [14] advocated histamine readings as an index of collateral circulation.

We have long been puzzled by the paradox of arteriosclerosis, in that although the blood pressure in an arm gradually increases, often to twice the value seen in health, yet the arm actually becomes smaller and atrophic. With this in mind, these experiments were devised to give, if possible, some quantitative expression of the progress of this disease.

All experiments were done at Cook County Hospital, in ward 15, on normal healthy men, medical students, interns and patients in the ward. Tracings were made from only three women (nurses).

METHOD

A small quiet room with a fairly even temperature of about 72 F. (22 C.) was found suitable for these tests. The subject was asked to elevate his hand above his head for a few minutes to insure a more complete emptying of the veins of the arm. An elastic 3 inch (7.6 cm.) Martin bandage was wound tightly about the arm, beginning at the fingers and proceeding spirally upward to 2 inches

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(5 cm.) above the elbow. It was always applied with uniform and maximum tension, often by the same person. A tourniquet was applied ½ inch (1.2 cm.) above the Martin bandage, just as a surgeon prepares an arm for amputation. As soon as the tourniquet was locked, the thin rubber bandage was removed and the arm was lightly dusted with powder and inserted into the plethysmograph. This instrument was of the usual construction, having a long brass tube fitted with several outlets and a flexible rubber cuff. An automobile inner tube of the size that fit the patient's arm worked admirably. A small rubber tube connected one outlet with a water manometer, which recorded directly on a smoked drum. All other outlets of the plethysmograph were closed during the experiments. After four or five minutes of occlusion, during which time an adequate control tracing and base line were obtained, the tourniquet was quickly released. A rapid regular rise was seen in the graph, followed by a sustained plateau. The drum was then stopped, and the increased volume of the system was measured by aspirating air from a Y tube between the manometer and the plethysmograph. This was generally recorded in 20 cc. quantities, but when there were small "reactions" it was marked in 10 cc. amounts. A uniform speed of 1.5 cm. per minute was maintained by the drum. Outlets were opened and the base line was verified. A small rubber band was snapped about the arm at the free margin of the cuff, and the arm was withdrawn from the plethysmograph. Total volume measurements of the arm were determined by the immersion method. Our brass cylinder was equipped with a small lead strip which was used as an indicator of the water level, serving in this dual capacity nicely.

In our early experiments, the type and the height of the curve were studied. Generally, with a large arm a large rise was seen, and a small arm gave a small curve, so this method was abandoned. To overcome this error, an expression of the amount of increased volume of a part after release of the compressed artery to a given unit of that extremity was sought. Let C represent the amount in cubic centimeters of increased volume of a part after the release of the tourniquet, and T the total volume of the part included in the plethysmograph. This simply resolves itself to: $\frac{C}{T}100$. Or, in other words, it is the percentage of the total compressibility of the vascularity of a part to that part.

RESULTS

Several tests were made on the same person (fig. 1). They were performed at intervals of one-half hour, since it was believed that all disturbing influences from previous compression would be abolished during that time. Ratios of the two arms were practically identical in several tests (table 1). In a series of twenty-four normal men (free from vascular disease), the ratios were from 4.5 to 8.8. Age apparently did not influence this ratio. The youngest, aged 20, and the oldest, aged 74, had figures of 5.2 and 5.3, respectively. Only three women were included, and while this number is too small for critical study, it is odd that their average was 5.9, as compared to 6 for the men. Errors incident to the method are great, so the ratios should be expressed only in the nearest tenths. In this group of twenty-seven normal persons, the lowest value was 4.4, and we arbitrarily accepted this as the lowest limit of normal. Smaller values were considered pathologic.

A group of thirty-one persons constituted the abnormal series (table 2). Six persons with diabetes gave values ranging from 4.5 to 8, all within the normal scope (fig. 2). Four of these cases were complicated by other disease: two by thyrotoxicosis, one by hypertension and early arteriosclerosis and one by bronze diabetes. Apparently, the additional pathologic condition was insufficient to disturb this ratio. There

TABLE 1.—*Normal Values for the Arms*

Case	Name	Sex	Age, Yrs.	T Total Volume		C Compressed Volume		Ratio $\frac{C}{T}$ 100	Diagnosis
				Right Arm	Left Arm	Right Arm	Left Arm		
1	S. P.	M	20	1,150	.....	60	..	5.2	Epilepsy
2	T. S.	M	23	1,470	.....	80	..	5.5	Gastritis
3	D. S.	M	24	1,675	.....	95	..	5.7	Normal
4	G. F.	M	24	1,500	.....	90	..	6.0	Normal
5	D. W.	M	25	1,700	.....	90	..	5.3	Normal
6	C. B.	M	26	2,040	.....	120	..	5.9	Psychoneurosis
7	H. L.	M	29	1,960	.....	130	..	6.6	Normal
8	C. E.	M	29	1,790	.....	80	..	4.5	Normal
9	J. P.	M	30	2,020	.....	110	..	5.5	Amebiasis
10	J. J.	M	31	1,460	.....	85	..	5.8	Multiple sclerosis
11	A. T.	M	34	1,890	.....	130	..	6.9	Syphilis
12	J. A.	M	35	1,550	.....	70	..	4.5	Unresolved pneumonia
13	P. B.	M	36	1,320	.....	60	..	4.5	Arthritis
14	S. T.	M	37	1,460	.....	80	..	5.4	Peptic ulcer
15	C. E.	M	37	1,360	.....	80	..	5.9	Rheumatic fever
16	R. R.	M	46	1,550	.....	90	..	6.0	Fibrous tuberculosis
17	A. B.	M	46	1,610	.....	100	..	6.2	Neurasthenia
18	A. M.	M	49	1,460	.....	120	..	8.2	Duodenal ulcer
19	J. H.	M	51	1,490	1,450	100	90	6.7/6.2	Argyria
20	M. S.	M	58	1,765	1,810	140	140	7.9/7.7	Arthritis
21	T. W.	M	63	1,580	.....	140	..	8.8	Chronic alcoholism
22	S. C.	M	65	1,320	.....	75	..	5.7	Arthritis
23	D. L.	M	73	1,640	.....	80	..	4.8	Cholelithiasis
24	G. R.	M	74	1,490	.....	80	..	5.3	Arthritis deformans
Mean average.....								6.05	
25	E. L.	F	27	1,140	.....	80	..	7.0	Normal
26	M. S.	F	28	1,460	.....	65	..	4.4	Normal
27	E. F.	F	33	1,020	.....	70	..	6.7	Peptic ulcer
Mean average.....								5.93	
Average for group.....								5.99	

were four persons with carcinomas who had ratios of 2.5, 2.7, 4 and 5.6. In the first two, the emaciation and cachexia probably accounted for these low values. Two patients with aortitis (fig. 3) gave ratios of 2.8 and 3.8, while a youthful patient with hypertension also gave 3.8. A patient with a syphilitic hemiplegia on the left side had a ratio of 2.7 in the paralyzed arm, and 3.4 in the other one (fig. 4).

Patients with nephritis gave low ratios except in one case, which showed a normal value. In two patients with acute exacerbation of chronic glomerulonephritis, the figures were 3.6 and 3.8 (fig. 5) while in two patients with long-standing cases of chronic nephritis they were 2.6 and 4.1 (fig. 6). A patient with chronic interstitial nephritis, a high

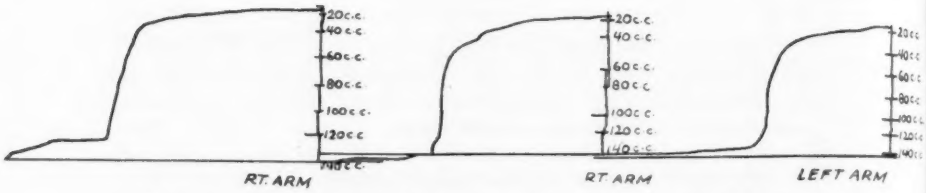

Fig. 1.—Tracings made on M. S., aged 58, suffering from arthritis but free from vascular disease. The first two tracings were taken within one-half hour of each other; that of the left arm in the next half hour. The total volume of the right arm was 1,765 cc.; the compressed volume, 140 cc. The total volume of the left arm was 1,810 cc.; the compressed volume, 140 cc. The ratios were: right arm, 7.9; left arm, 7.7.

Fig. 2.—Tracing made on O. H., aged 37, with diabetes, hypertension and early arteriosclerosis. The blood pressure was 180 systolic and 120 diastolic. The total volume of the arm was 1,935 cc.; the compressed volume, 110 cc. The ratio was 5.7.

Fig. 3.—Tracing made on F. P., aged 47, with aortitis and aortic regurgitation. The total volume of the arm was 1,280 cc.; the compressed volume, 35 cc. The ratio was 3.8.

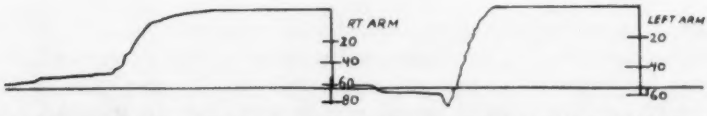

Fig. 4.—The first tracing was made on T. A., aged 34, with syphilitic hemiplegia on the left. The first tracing is of the right arm; the total volume was 1,890 cc.; the compressed volume, 65 cc.; the ratio was 3.4. The second tracing is of the paralyzed arm; the total volume was 1,780 cc.; the compressed volume, 50 cc.; the ratio was 2.7.

grade hypertension and retinitis albuminurica had the lowest ratio of this group, 2.5.

Patients with arteriosclerosis gave very low ratios, although there was one case that might be classed as normal. A markedly arteriosclerotic patient, aged 55 years, the youngest of these men, had a ratio

TABLE 2.—*Values for Different Diseased Conditions*

Case	Name	Sex	Age, Yrs.	T Total Volume Right Arm	T Total Volume Left Arm	C Compressed Volume Right Arm	C Compressed Volume Left Arm	Ratio $\frac{C}{T}100$	Diagnosis
1	F. H.	M	24	1,930	1,775	100	80	5.1/4.5	Diabetes and thyroid disease
2	H. J.	M	25	1.510	.....	120	..	8.0	Diabetes
3	R. R.	M	27	1,720	.....	100	..	5.8	Diabetes and thyrotoxicosis
4	J. W.	M	29	1,900	.....	110	..	5.8	Diabetes
5	O. H.	M	37	1,935	.....	110	..	5.7	Diabetes and early arteriosclerosis
6	H. N.	M	52	2,150	.....	90	..	4.2	Toxic adenomatomas
7	G. P.	M	65	1,420	.....	65	..	4.5	Bronze diabetes
8	J. W.	M	48	1,950	.....	110	..	5.6	Branchiogenic cancer
9	J. B.	M	58	1,480	.....	60	..	4.0	Branchiogenic cancer
10	J. S.	M	61	1,460	.....	40	..	2.7	Cancer of pylorus
11	N. M.	M	73	1,200	.....	30	..	2.5	Cancer of rectum
12	F. P.	M	47	1,280	.....	35	..	3.8	Aortitis and aortitic regurgitation
13	W. J.	M	53	1,630	.....	45	..	2.8	Aortitis
14	W. G.	M	15	1,420	.....	55	..	3.8	Youthful hypertension
15	A. V.	M	48	1,360	1,340	75	85	5.5/6.3	Intermittent claudication
16	T. A.	M	34	1,890	1,780	65	50	3.4/2.7	Left hemiplegia
17	B. R.	M	22	1,375	.....	50	..	3.6	Acute exacerbation of chronic nephritis
18	J. M.	M	63	1,600	.....	40	..	2.5	Retinitis albuminurica
19	T. B.	M	65	1,920	.....	80	..	4.1	Chronic nephritis
20	P. P.	M	62	1,720	.....	45	..	2.6	Chronic nephritis
21	W. W.	M	43	1,320	.....	50	..	3.8	Acute exacerbation of chronic nephritis
22	W. B.	M	55	1,785	.....	35	..	1.97	Marked arteriosclerosis
23	J. S.	M	58	1,400	.....	40	..	2.9	Arteriosclerosis and sclerosis of coronary arteries
24	W. K.	M	58	2,080	.....	60	..	2.9	Arteriosclerotic heart
25	H. B.	M	64	1,130	.....	45	..	4.0	Arteriosclerotic heart
26	J. F.	M	64	1,525	.....	45	..	3.0	Arteriosclerosis; diabetes
27	G. B.	M	65	1,810	.....	80	..	4.4	Arteriosclerotic heart; decompensation
28	J. H.	M	76	1,440	.....	50	..	3.5	Arteriosclerosis
				Right Leg	Left Leg	Right Leg	Left Leg		
29	H. L.	M	29	2,060	.....	200	..	9.7	Normal
30	A. V.	M	48	2,060	2,000	130	90	6.3/4.5	Intermittent claudication
31	S. C.	M	53	2,520	2,560	130	120	5.1/4.7	Diabetes; arteriosclerosis; ulcers on both legs
32	E. H.	M	74	2,250	.....	40	..	1.76	Dry gangrene on right leg

of 1.9. Three patients with arteriosclerotic hearts had ratios of 2.9, 3.5 and 4, and one whose condition was complicated by definite involvement of the coronary artery had 2.9 (fig. 7). A patient with diabetes and arteriosclerosis had a ratio of 3, while another with a decompensated heart had 4.4, a value that might be classed as normal. This group as a whole showed the most noticeable lowering of the ratio.

Tracings of the leg were made on only four persons, and these results are added since they indicate a similar change in the leg to that in the arm. A ratio of 9.7 (fig. 8) was found in a normal person, and one with an intermittent claudication (fig. 9) gave 4.5 and 6.3. This patient

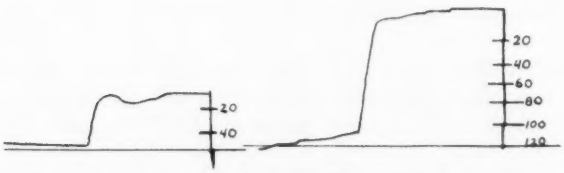

Fig. 5.—The first tracing was made on W. W., aged 43, with acute exacerbation of a chronic glomerular nephritis; the total volume of the arm was 1,320 cc.; the compressed volume, 50 cc.; the ratio was 3.8. The second tracing was obtained on A. M., aged 49, with a duodenal ulcer; the total volume of the arm was 1,460 cc.; the compressed volume, 120 cc.; the ratio was 8.2.

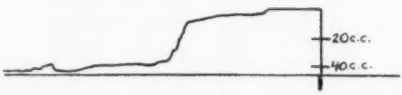

Fig. 6.—Tracing made on P. P., aged 62, with chronic nephritis. The total volume of the arm was 1,720 cc.; the compressed volume, 45 cc.; the ratio was 2.6.

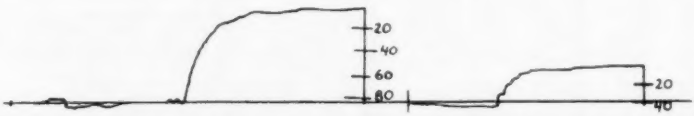

Fig. 7.—The first tracing was made on G. R., aged 74, with arthritis; the total volume of the arm was 1,490 cc.; the compressed volume, 80 cc.; the ratio was 5.3. The second tracing was obtained on J. S., aged 58, with coronary sclerosis; the total volume of the arm was 1,400 cc.; the compressed volume, 40 cc.; the ratio was 2.9.

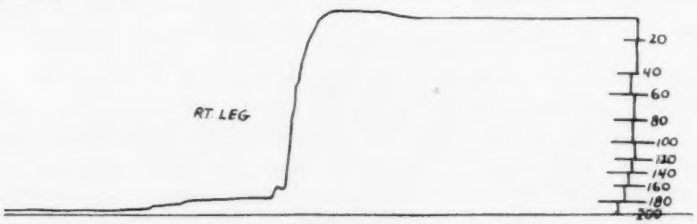

Fig. 8.—Tracing made on H. L., aged 29, a normal subject. The total volume of the leg was 2,060 cc.; the compressed volume, 200 cc. The ratio was 9.7.

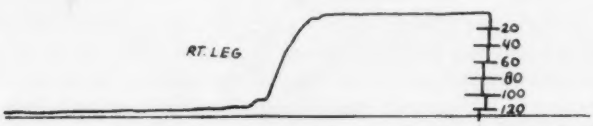

Fig. 9.—Tracing made on A. V., aged 48, with intermittent claudication. The total volume of the leg was 2,060 cc.; the compressed volume, 130 cc. The ratio was 6.3.

complained of more distress, cramps and pain in the left calf, the leg with the lower ratio. A patient with diabetes and ulcers on both legs, awaiting amputation, had a ratio of 5.1 and 4.7, and a patient with a self-amputating dry gangrene of the right great toe and arteriosclerosis gave only 1.7.

COMMENT

The method was critically examined by us, and all sources of error were appraised. First the Martin bandage was applied several times, and approximately the same increase in volume was noted. Several tests were made on the same subject on different days, and the error was within 20 cc. Second, the increase in air pressure was questioned as representing the increase in air volume. An arm was prepared in the usual way, then immersed in water, and the volume was noted. The tourniquet was then released, and the new volume was recorded. This increase roughly equaled the increase shown on a graph made later. Appreciation of the crudeness of the immersion method is necessary in evaluating these results. Third, many tracings had a small but gradual elevation during the control period. In earlier tracings, this was entirely eliminated by placing the left forearm in the plethysmograph prior to the experiment, thus warming it. As it was our object to have the rubber cuff fit as loosely as possible on the arm and cause no venous obstruction, many attempts were failures, as the cuff was not air-tight. To insure an air-tight system, this rise due to heat was welcomed as a check on the system; proper deductions of it were made later. Fourth, in some tracings, a depression and an irregular rise were displayed before the sustained high rise. They were movements of the arm in the plethysmograph incident to the removal of the tourniquet. Fifth, only a few patients showed muscular contractions of sufficient magnitude to interfere with the graph, but at no time did they obscure the levels. It must be added that our earliest attempts were disheartening, as they recorded all muscular movements, tremors and pulse waves. The instrument was made less sensitive, obliterating these curves and writing fairly regular curves which were easier to evaluate. Patients were seated with the arm in a horizontal position, the elbow properly supported and comfortably adjusted, so that most of them, even the very sick, had no difficulty in remaining quiet during the test.

Our results agree well with those of Hewlett and Van Zwaluwenburg,[15] who studied the rate of blood flow to the arm following venous obstruction. Tschuewsky[16] actually measured the blood flow to a dog's

15. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, Heart **1**:87, 1909.

16. Tschuewsky, J. A.: Ueber Druck, Geschwindigkeit und Widerstand in der Strombahn der Arteria Carotis und Cruralis sowie in der Schilddrüse und in dem Musculus gracilis des Hundes, Arch. f. d. ges. Physiol. **97**:210, 1903.

hindleg by a *Stromuhr*. He found that after a brief arterial obstruction 6.89 cc. of blood flowed per hundred cubic centimeters of leg. Sir Thomas Lewis, in his painstaking work on "reactive hyperemia," studied the effect of heat and cold, duration of obstruction and exercise on this phenomenon, but did not apply the test to any pathologic cases.[17]

Admitting from the outset the simplicity and crudeness of this apparatus, we believe this test is of value in the study of peripheral vascular disease. This paper is to be viewed only as a preliminary report; further work is now in progress.

CONCLUSIONS

1. A test of the total compressible vascularity of a part is described, and a ratio is used to express it.

2. Normal ratios vary from 4.4 to 8.8.

3. Ratios lower than 4.4 were considered pathologic.

4. Cases of diabetes, thyrotoxicosis, aortitis, hypertension, carcinoma, nephritis and arteriosclerosis were studied.

17. Lewis, T., and Grant, R. T.: Observations on Reactive Hyperemia, Heart **12**:73, 1925.

CIRCULATORY DYNAMICS IN MYOCARDIAL INFARCTION

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The clinical evidences of circulatory failure in the first days of myocardial infarction often differ conspicuously from the manifestations of decompensation in other diseases of the heart. In many instances the absence of orthopnea is striking; the patient evinces no distress when lying flat in bed despite the fact that grayish cyanosis and cold extremities testify to the impairment of the peripheral circulation. Moreover, inspection of the cervical and other superficial veins reveals that they are largely collapsed. These observations are in sharp contrast to those which one is accustomed to encounter when equally severe retardation of the peripheral circulation occurs in such conditions as, for example, mitral stenosis. In that case the patient is orthopneic, and the superficial veins are engorged. The picture in myocardial infarction is obviously the one which is familiar to every physician under the name of shock and which results from disturbances in the periphery of the circulation with a resultant decrease in the venous return to the heart. The remarkable feature is that this exquisitely peripheral type of failure results from myocardial infarction, a cardiac lesion *par excellence*.

In other instances of myocardial infarction the consequences of cardiac rather than peripheral circulatory failure are dominant. They may consist of manifestations of insufficiency of the left side of the heart, largely orthopnea and other consequences of pulmonary stasis, or the right side may fail, with resultant swelling of the systemic veins and of the liver. Most often, evidences of both cardiac and peripheral circulatory failure are present.

In this communication we present observations relevant to the nature of the derangements in the dynamics of the circulation underlying these diverse clinical pictures of myocardial infarction.

From the Medical Services and the Laboratories of the Mount Sinai Hospital.

* Eugene Meyer Fellow. Aided by a grant to the Emanuel Libman Fellowship Fund in memory of Adele Schiff.

** Emanuel Libman Fellow.

MATERIAL AND METHODS

Fifty-nine patients with clinical and electrocardiographic evidence of recent myocardial infarction were observed. Twenty-six cases were fatal and necropsy was performed in nineteen. In addition to the usual clinical observations, the venous pressure, circulation time and volume of the circulating blood were studied.

Venous Pressure.—This was measured by the method of Taylor, Thomas and Schleiter,[1] with slight modifications.

The apparatus is an L-shaped glass tube 30 cm. in length and 4 mm. in bore. The short limb is ground to fit a 19 gage needle. The manometer is sterilized by boiling, and moistened with a 10 per cent solution of sodium citrate. The latter serves to inhibit coagulation during protracted measurements and minimizes the resistance to the flow of blood in the tube.

The patient is placed in the supine position. He is cautioned to relax and breathe as usual. The relaxed upper extremity is extended parallel to the mid-axillary line and propped up throughout its length by a pillow so that an antecubital vein is 5 cm. below the anterior surface of the sternum at the attachment of the fourth rib. This is approximately the level of the caval openings in the right auricle.

The cuff of the sphygmomanometer is applied above the elbow and inflated to 30 or 40 mm. of mercury. Immediately after insertion of the needle into the vein, the constricting cuff is deflated. The height attained by the column of blood in the tube is the venous pressure in centimeters of blood. A confirmatory reading is generally obtained by again inflating the cuff so that the blood in the tube rises above the level of the venous pressure. On releasing the cuff, the blood flows back into the vein until the column has fallen to the level of the venous pressure. The "blood up" and "blood down" readings should check closely.

In health, the pressure obtained by this method in a large antecubital vein is between 4 and 8 cm. of blood.

Circulation Time.—The method used was that of Fishberg, Hitzig and King.[2] Two and five-tenths grams of soluble gluside is dissolved by heating in 2 cc. of sterile distilled water. It is taken up in a 5 cc. syringe attached to a 19 gage needle and allowed to cool spontaneously to body temperature. The patient reclines in bed in a position which is as nearly flat as comfortable. He is instructed to relax and not to hold his breath following the insertion of the needle. He is also told that he will experience a sweet taste, which he should announce immediately. The arm is supported on a pillow as for the determination of the venous pressure. A tourniquet is applied just before the insertion of the needle into a large antecubital vein and removed as soon as the needle is in the vein. After waiting about a minute for any circulatory disturbance consequent on the venipuncture and application of the tourniquet to subside, the injection is performed as rapidly as feasible. The time elapsing between the injection and the perception of the sweet taste is recorded with a stop-watch. The subject usually describes the sweet taste as passing with great rapidity from the base to the tip of the tongue and quickly diminishing.

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1. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: Direct Method for Estimation of Venous Blood Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867 (May) 1930.

2. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Measurement of Circulation Time with Saccharin, Proc. Soc. Exper. Biol. & Med. **30**:651 (Feb.) 1933.

By this method, the circulation time in health is between nine and sixteen seconds. The circulation time thus determined is largely a measure of the velocity of blood flow through the lungs, for there is evidence to show that comparatively little time is taken for the blood to flow from the antecubital vein to the right side of the heart and from the left side of the heart to the capillaries of the tongue. The only complete capillary circuit traversed is that in the lungs. In accordance with this, we have found that great prolongation of the circulation time as tested by the gluside method is most common in failure of the left side of the heart with pulmonary engorgement. On the other hand, in the peripheral circulatory failure of shock, the time, when tested by gluside, is much less prolonged or even within normal limits.

The Volume of Circulating Blood.—This was determined by the injection of congo red. The results in health are between 70 and 95 cc. per kilogram of body weight.

The observations are recorded in table 1. The caption "duration of infarction" indicates the time between the onset of the first symptom that seemed definitely indicative of myocardial infarction and the time when the first circulatory measurements were carried out. This is only approximate, for in many instances the symptoms set in gradually. In the column headed "localization of fresh infarction," the site of the most recent infarction is described. The site of fresh infarction was determined at necropsy in nineteen cases.

In the remainder, the electrocardiographic criteria developed by Barnes and Whitten,[3] Pardee and Bell,[4] Crawford and his associates,[5] Wilson and his co-workers,[6] Fenichel and Kugell,[7] and Wolferth and his associates[8] were used to establish the general localization of the recent infarction. This electrocardiographic localization is expressed in the table as either anterior or posterior infarction. By anterior infarction is meant involvement of the anterior and apical portions of the left ventricle, which often extends far enough to the right to implicate the anterior third of the septum and the adjacent anterior and apical portion

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3. Barnes, A. B., and Whitten, M. B.: Study of the R T Interval in Myocardial Infarction, Am. Heart J. **5**:142 (Dec.) 1929.

4. Pardee, H. E. B., and Bell, A.: Report of Two Cases with Electrocardiographic Localization of the Thrombus in the Right or Left Coronary Arteries, J. A. M. A. **94**:1555 (May 17) 1930.

5. Crawford, J. H.; Roberts, G. H.; Abramson, D. I., and Cardwell, G. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, Am. Heart J. **7**:627 (June) 1932.

6. Wilson, F. N.; MacLeod, A. G.; Barker, P. S.; Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, Heart **16**: 155 (June) 1933.

7. Fenichel, N. M., and Kugell, V. H.: Large Q-Wave of Electrocardiogram, Am. Heart J. **7**:235 (Dec.) 1931.

8. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933.

TABLE 1.—*Circulatory Measurements in Myocardial Infarction*

Case	Duration of Infarction	Date	Venous Pressure, Cm. of Blood	Circulation Time, Sec.	Circulating Blood Volume Cc./Kg.	Arterial Pressure, Mm. Hg	Localization of Fresh Infarction	Outcome
1*	5½ hrs.	7/17	9	19½	101	110/ 80	Posterior (ecg.†)	
		7/26	8	..	..	110/ 74		
		7/31	6	17	105	114/ 70		
		8/ 4	6	15½	..	112/ 70		Improved
2	18 hrs.	3/10	10.5	18½	..	140/ 96	Equivocal (ecg.)	
		3/11	5.5	..	82	120/ 96		
		3/12	8.5	17	..	110/ 80		
		3/13	7.5	..	..	130/100		
		3/16	8.5	20½	..	130/ 86		
		3/23	6.5	19¼	..	148/110		
		3/28	8.5	16¼	..	114/ 86		
		4/11	6.5	16½	..	98/ 78		
		4/20	6.5	15¾	..	118/ 90		Improved
Readmission		10/ 7	13	29	104	104/ 88		
		10/17	15	27	..	110/ 80		
		10/24	8.5	23	..	110/ 80		Improved
3	1 day	6/ 5	3.5	..	..	112/ 70	Anterior (ecg.)	
		6/13	9.5	..	..	104/ 68		
		6/24	7	..	..	98/ 64		Improved
4	1 day	11/25	12.5	25	..	96/ 70	Posterior (ecg.)	
		11/26	8	28	94	102/ 76		
		12/ 6	8	29	..	100/ 58		Improved
5	2 days	12/16	2.5	21	56	96/ 54	Equivocal (ecg.)	
		12/19	6.5	..	..	92/ 54		
		1/ 2	5.5	..	..	88/ 52		Improved
Follow-up		5/ 3	7	14½	..	148/ 90		No symptoms
6	2 days	6/ 8	5.5	14¼	..	110/ 84	Anterior (ecg.)	
		6/14	5.5	13½	..	112/ 90		Improved
7	3 days	11/ 1	12	41	65	80/ 60	Myomalacia of anterolateral, septal, apical and basal portions of left ventricle; postmortem	Died; postmortem
8	6 days	7/30	1.5	..	..	140/ 84	Equivocal (ecg.)	
		8/ 2	2	..	..	140/ 86		
		8/ 4	5	..	..	142/ 80		
		8/ 6	1.3	..	..	116/ 62		
		8/ 6	4.5	..	..	124/ 72		
		8/ 8	5	..	..	122/ 86		
		8/18	4	..	..	102/ 70		
		8/26	5.5	..	..	140/ 80		
		9/ 6	6	..	..	144/ 84		Improved
9	6 days	11/22	2.5	11½	79	122/ 80	Anterior (ecg.)	Died; no autopsy
		11/26	3	11¾	73	114/ 76		
10	6 days	2/ 8	3.5	32	72	130/100	Anterior (ecg.)	
		2/ 9	2.5	..	..	128/ 92		
		2/11	7.75	24	..	110/ 80		
		2/16	5	..	..	125/ 90		
		2/19	4	..	..	120/ 86		
		2/21	2.5	..	..	126/ 90		
		2/23	5.5	..	..			
		2/27	8	..	85	110/ 90		
		3/ 4	4.5	18½	..	126/ 90		
		3/12	3	22	..	120/ 94		
		3/16	4.5	..	..	118/ 90		
		3/28	5	19¼	..	128/ 96		
		4/25	6	18	..	132/ 96		
		5/12	7	23	..	130/ 94		Improved
Readmission		6/27	6.5	29	102	126/ 90	Anterior (ecg.)	Improved
Readmission		11/ 6	10	39	110	146/104		Improved
11	7 days	11/17	2.5	..	..	100/ 68	Posterior (ecg.)	
		11/20	3	..	..	112/ 58		
		11/24	3.25	..	..	100/ 50		
		11/27	2.5	..	..	114/ 60		Improved

* Cases 1 to 16 inclusive were instances of initial myocardial infarction, while in cases 17 to 59 inclusive there was notable cardiac insufficiency prior to the present infarction.

† Electrocardiogram.

TABLE 1.—*Circulatory Measurements in Myocardial Infarction—Continued*

Case	Duration of Infarction	Date	Venous Pressure, Cm. of Blood	Circulation Time, Sec.	Circulating Blood Volume Cc./Kg.	Arterial Pressure, Mm. Hg	Localization of Fresh Infarction	Outcome
12	9 days	12/22	18	..	90	142/ 90	Myomalacia of apex, both papillary muscles and lower portion of septum of left ventricle; perforation of septum	Died; autopsy
		12/25	22.5	..	..	96/ 72		
13	11 days	4/24	6	10½	..	220/110	Posterior (ecg.)	
		5/ 5	5.5	11	..	168/ 98		Improved
14	14 days	7/ 8	2	18½	49	118/ 80	Anterior (ecg.)	
		7/18	1	19½	..	160/110		
		7/20	2	..	73	176/110		
		8/16	4.5	16	..	116/ 84		Improved
15	1 to 8 weeks	2/27	6	18½	..	120/ 80	Anterior (ecg.)	
		3/ 3	5	19	..	102/ 76		Improved
16	8 weeks (repeated attacks)	8/26	3.5	..	..	98/ 74	Anterior and apical portion of left ventricle	Died; autopsy
		8/29	4	..	..	106/ 78		
		9/ 4	3.5	..	..	96/ 72		
17	15 hours	6/ 6	3.5	14	82	96/ 70	Equivocal (ecg.)	
		6/10	6	..	..	130/ 94		Improved
18	1 day	5/20	8.5	..	..	.....	Posterior (ecg.)	
		5/25	8	42	..	200/140		
		5/29	..	49	..	180/130		
		5/31	6.5	36	..	178/ 98		Improved
	Readmission 7 days	7/26	20	..	..	136/ 80		Died; no autopsy
19	1 day	6/ 7	2.5	..	..	96/ 76	Posterior basal portion of left ventricle	Died; autopsy
20	1 day	10/6/32	2	..	..	130/ 88	Posterior (ecg.)	
		10/ 7	6.5	..	..	160/106		
		10/ 7	4	..	..	210/140		Improved
	Readmission	11/28/33	20	..	..	184/118		
		11/29	18.5	42	105	168/108		In hospital
21	1 day	9/27	8.5	..	..	150/ 92	Posterior (ecg.)	
		9/30	11	..	..	180/110		
		10/ 3	8	..	..	160/ 90		
		10/10	6	..	..	146/ 84		Died; no autopsy
22	1 day	7/ 7	3	19	..	112/ 88	Posterior (ecg.)	
		7/ 8	4.5	..	94	98/ 70		
		7/18	9.5	13½	..	120/ 90		Improved
23	1 day	5/30	10.5	23¾	..	174/ 94	Posterior (ecg.)	Improved; died 4 mos. later
		6/ 9	6	18½	..	172/ 80		
24	1 day	10/ 4	5	..	68	106/ 80	Anterior (ecg.)	
		10/ 6	6	..	..	92/ 76		Improved
25	1 day	8/25	12.5	..	..	90/ 60	Anterior (ecg.)	
		8/26	9.5	..	..	96/ 70		
		8/28	6.5	..	..	102/ 70		
		8/31	4	..	..	86/ 56		
		9/ 1	3	..	..	94/ 56		
		9/ 2	3.25	..	..	96/ 56		
		9/ 4	3.5	..	..	104/ 60		
		9/ 6	3.5	..	..	96/ 60		Improved
26	1 day	4/17	19	..	..	170/130	Posterior basal portion and septum of left ventricle	Died; autopsy
27	1 day	7/22	17.5	29	..	120/ 80	Posterior (ecg.)	
		8/17	4.5	15	..	146/ 86		Improved
28	1 day	10/28	10	..	..	120/ 90	Anterior (ecg.)	
		10/29	7.5	..	..	106/ 80		
		10/30	4.5	..	..	94/ 78		
		10/31	6.75	..	..	104/ 78		
		11/ 3	8	..	..	92/ 72		
		11/ 6	9.5	..	..	104/ 84		
		11/ 9	8.75	..	..	110/ 84		
		11/10	7	25	..	114/ 92		
		11/14	6	..	..	106/ 90		
		11/21	7.5	..	..	110/ 90		
		11/24	6.25	..	..	124/ 94		Improved

TABLE 1.—*Circulatory Measurements in Myocardial Infarction—Continued*

Case	Duration of Infarction	Date	Venous Pressure, Cm. of Blood	Circulation Time, Sec.	Circulating Blood Volume Cc./kg.	Arterial Pressure, Mm. Hg	Localization of Fresh Infarction	Outcome
29	2 days	4/18	3	16½	..	122/ 74	Equivocal (ecg.)	Unimproved; discharged against advice
30	2 days	12/30	8	..	98	118/ 76	Posterior (ecg.)	Unimproved; psychotic transferred
		1/ 1	10	..	..	124/ 80		
		1/11	8.5	..	..	108/ 72		
		2/ 3	7	..	..	80/ 56		
31	2 days	9/25	4.5	32	..	125/ 85	Anterior and apical portions of left ventricle; anterior and apical portions of right ventricle	Died; autopsy
32	3 weeks	1/11	3	..	..	110/ 70	Equivocal (ecg.)	
		1/14	4	..	..	112/ 72		
		1/16	4	..	..	170/ 90		Improved
Readmission								
	2 days	8/ 9	12	27¼	77	80/ ?	Anterior apical and septal portions of left ventricle	Died; autopsy
		8/10	16	..	..	82/ ?		
		8/13	8.5	..	..	120/ ?		
		8/21	9	26	..	100/ ?		
		8/28	7	..	..	102/ ?		
		9/ 5	8.5	30	70	106/ ?		
33	2 days	8/21	3	33½	120	140/100	Equivocal (ecg.)	Died; no autopsy
		8/26	2.5	30	..	120/ 80		
		8/30	3.5	32	..	110/ 76		
34	2 days	4/ 4	10.5	..	..	180/130	Equivocal (ecg.)	Died; no autopsy
		4/ 6	13.5	45½	114	130/100		
35	3 days	11/22	15.5	..	..	86/ ?	Posterior basal portion and septum of left ventricle	Died; autopsy
		11/23	15.75	..	96	80/ ?		
36	3 days	4/14	14	36	..	80/ 56	Posterior, basal, posterolateral, anterior apical and anterolateral portions of left ventricle	Died; autopsy
		4/15	19	..	..	78/ 52		
37	3 days	8/17	2.5	..	..	118/ 64	Posterior (ecg.)	
		8/18	5	..	..	130/ 56		
		8/20	3	..	..	134/ 68		
		8/21	2.5	..	..	114/ 60		
		8/22	3.5	..	..	130/ 66		
		8/24	2	..	..	120/ 62		
		8/25	3	..	..	130/ 66		
		8/27	2.5	..	..	132/ 76		
		8/28	4.5	38	..	130/ 74		Improved
38	4 days	2/ 4	3	24	..	130/ 90	Equivocal (ecg.)	
		2/ 6	4.5	22	92	108/ 80		
		2/ 7	1.5	..	..			
		2/ 8	3	..	..			
		2/13	6.5	36	..	108/ 76		
		2/17	5.5	24½	..	114/ 88		Improved;
Readmission		11/29	6.5	38	..	150/100		in hospital
39	4 days	5/15	6	29	75	92/ 76	Posterior (ecg.)	Died; no autopsy
		5/17	5.5	34	..	70/ ?		
		5/18	12	..	..	70/ ?		
40	4 days	3/31	6	13½	98	110/ 70	Equivocal (ecg.)	
		4/ 8	6.5	14	..	116/ 82		Improved
41	4 days	4/13	8.5	40	108	118/ 64	Anterior apical and septal portions of left ventricle	Died; autopsy
		4/18	8	39	..	100/ 60		
		4/21	5.5	42	..	150/ 98		
		4/26	7.5	35¾	..	90/ 56		
		5/28	12	..	..	114/ 70		

TABLE 1.—*Circulatory Measurements in Myocardial Infarction—Continued*

Case	Duration of Infarction	Date	Venous Pressure, Cm. of Blood	Circulation Time, Sec.	Circulating Blood Volume Cc./Kg.	Arterial Pressure, Mm. Hg	Localization of Fresh Infarction	Outcome
42	4 days	8/ 4	2.5	..	..	90/ 64		Improved
		8/ 6	5.5	..	..	86/ 62		
	Readmission 10 days	9/12	18	..	..	104/ 88	Posterior basal	Died; autopsy
		9/13	20	..	..	104/ 88	and septal portions	
		9/14	5	..	..	118/ 70	of left ventricle	
		9/15	4	..	..	104/ 74		
		9/16	2.5	..	..	102/ 70		
43	5 days	12/ 9	16	..	..	96/ 70	Anterior apical	Died; autopsy
		12/11	14.5	..	..	86/ ?	and septal portions	
							of left ventricle	
44	5 days	8/31	2.5	..	81	140/ 94	Posterior (ecg.)	Died; no autopsy
		9/ 1	2	..	..	126/ 90		
	Fresh infarction	9/ 2	3.5	..	..	126/ 80		
		9/ 4	12	..	..	78/ 60		
		9/ 4	11.5	..	..	88/ 68		
		9/ 5	13	..	..	88/ 72		
		9/ 6	15.5	..	..	80/ ?		
45	6 days	11/22	4	..	..	110/ 80	Posterior (ecg.)	
		11/27	6	23	..	130/ 84		Improved
46	6 days	11/28	9.5	..	114	92/ 76	Posterior basal,	Died; autopsy
		11/30	9	..	..	100/ 80	anterolateral, and	
		12/ 2	8.5	..	..	88/ ?	anterior portions	
		12/ 6	15.5	..	..	118/ 90	of left ventricle	
		12/12	9	..	..	112/ 80		
		12/17	11	..	..	108/ 86		
		1/ 3	9.5	..	..	86/ 56		
		1/ 5	9.5	..	..	108/ 80		
47	7 days	8/ 7	2	..	..	84/ 58	Posterior (ecg.)	
		8/10	4	..	..	106/ 64		
		8/15	5	..	..	90/ 62		Improved
48	8 days	4/26	19	31	..	178/114	Posterior basal	Died; autopsy
		4/27	17	..	113	172/110	portion of left	
							ventricle and septum	
49	9 days	2/ 7	3.5	51¾	127	132/ 90	Posterior (ecg.)	Improved; does light work
		2/ 9	6.5	60½	..			
	Follow-up	4/ 4	7.5	39	..	156/ 94		
50	2 weeks	8/12	3.5	16¼	114	86/ 66	Posterior (ecg.)	
		8/20	4.5	13	..	86/ 60		Improved
51	2 weeks	3/28	7	11¼	118	126/ 96	Equivocal (ecg.)	
		4/ 8	8	12	..	120/ 86		Improved
52	2 weeks	4/10	26	..	..	192/110	Anterior, posterior	Died; autopsy
							apical and septal	
							portions of left	
							ventricle	
53	2 weeks	8/29	11.5	..	..	120/ 68	Posterior, basal,	Died; autopsy
							septal and both	
							papillary muscle	
							portions of left	
							ventricle	
54	3 weeks	6/10	7.5	15	..	164/120	Posterior (ecg.)	Improved
55	3 weeks	12/22	17	..	..	160/100	Posterior basal	Died; autopsy
		12/28	12	..	..	110/ 80	and anterior apical	
		12/29	5.5	..	..	140/ 94	portions of left	
		12/30	6	..	..	120/ 80	ventricle	
56	3 weeks	7/23	7.25	..	..	128/ 82	Equivocal (ecg.)	
		8/ 9	7.5	..	..	142/ 96		Improved
57	4 weeks	7/26	7.5	35½	111	120/ 90	Anterior apical	Died; autopsy
		7/29	8.5	37	..	110/ 80	portion of left	
		8/15	8.5	36	120	120/100	ventricle	
58	4 weeks	4/21	23.5	47	122	194/104	Posterior (ecg.)	
		5/25	25.5	34¼	..	190/140		
		6/22	17.5	39	..	200/114		
		7/20	20	37	..	186/110		
		7/26	19	36	..	170/ 80		Improved
59	3 months	1/17	19.5	..	..	.....	Anterolateral	Died; autopsy
		1/18	19	..	..	140/110	portion of right	
		1/23	14	..	..	170/112	ventricle near base	

of the right ventricle (T_1 type of Parkinson and Bedford,[9] Q_1T_1 type of Wilson and his associates [6] due to thrombosis along the left coronary system). By posterior infarction is meant a lesion of the posterior and basal portion of the left ventricle, which often also involves the posterior two thirds of the interventricular septum and the adjacent posterior portion of the right ventricle (T_3 type of Parkinson and Bedford, Q_3T_3 type of Wilson,[6] usually due to thrombosis along the right coronary system). The electrocardiographic criteria seemed adequate for such general localization in thirty-one of the forty cases that did not come to postmortem examination.

VENOUS PRESSURE

The venous pressure was measured in all the patients. In most instances, repeated measurements were carried out, and in some the opportunity was afforded of studying the venous pressure during subsequent admissions.

TABLE 2.—*Venous Pressure in Myocardial Infarction*

Venous Pressure, Cm. of Blood	Initial Infarction		Previous Infarction or Severe Heart Failure	
	Cases	Deaths	Cases	Deaths
Less than 4	8	2	11	3
4 to 8	5	0	16	6
More than 8	3	2	16	13

As is seen in table 1, the venous pressure in myocardial infarction varies from subnormal levels to as high as 26 cm. It will be shown later that in the last analysis the height of the venous pressure in myocardial infarction is determined by whether shock or heart failure is predominant in the particular case. Early in the investigation it became evident that the previous functional capacity of the heart is one of the main factors determining which of these is predominant. The venous pressure was most often subnormal in what may be termed initial myocardial infarction, i. e., cases which do not present a history of antecedent myocardial infarction and in which the patient has not previously been incapacitated by heart failure, although there may have been anginal pains or dyspnea on exertion as manifestations of the underlying coronary arteriosclerosis. On the other hand, venous pressure was most often elevated or normal in myocardial infarction affecting persons who had previous similar episodes or who were suffering from severe heart failure prior to the present attack. This is illustrated in table 2, which shows the venous pressure on the first measurement in our fifty-nine patients.

9. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), Heart **14**:195, 1928.

In Initial Myocardial Infarction.—The venous pressure was subnormal in eight of the sixteen patients with initial myocardial infarction. In only three was it above the upper limit of normal. It is significant that in each of these three patients with high venous pressure in initial infarction, the interventricular septum was involved. In case 12, perforation of the septum had occurred; in case 7, complete heart block developed, and in case 4, septal involvement was revealed by prolongation of the auriculoventricular conduction time to 0.27 second.

Comparison of the venous pressure with the other clinical findings revealed that, as might be anticipated, low venous pressure is encountered especially in patients who present the clinical picture of shock. Venous hypotension is predominantly a feature of the early phases of myocardial infarction. In most cases, as the other manifestations of shock clear up, the veins can be seen to fill, and the pressure within rises to normal or elevated levels. This is the usual sequence of events in initial myocardial infarction that pursues a favorable course, and may be illustrated by a typical case.

CASE 22.—A man of 48 years was admitted, with the history of suffering from precordial pain and dyspnea on exertion for about a year. On the morning of the day of admission, while at work he was suddenly seized with an extremely severe pain in the left side of the chest anteriorly and posteriorly which radiated to the left axilla and shoulder. The pain continued for several hours, with accompanying weakness, chilliness, sweating and a sense of impending death.

On admission, the patient was able to lie flat in bed. He was cyanotic, but not notably dyspneic, breathing eighteen times per minute. While the superficial veins of the neck and upper extremities could be seen, they were collapsed, and did not fill out when strong pressure was exerted on the right upper quadrant. The temperature was 98 F., but soon rose to 101 F. Gallop rhythm was audible at the apex. Neither basal second sound was accentuated, that at the pulmonic area being weaker than that at the aortic area. A few fine râles were audible at the left base posteriorly. The electrocardiogram revealed evidence of recent infarction of the posterior portion of the left ventricle: The R T interval was elevated above the base-line in the third lead and slightly in the second lead, the T wave was inverted in the second and third leads and there was a large, broad Q wave in the second and third leads. Circulatory measurements were: arterial pressure, 98 systolic and 70 diastolic; venous pressure, 3 cm. of blood; circulation time, 19.5 seconds.

The patient improved steadily, the manifestations of shock disappearing in a few days. Two days after admission, the venous pressure was 4.5 cm. Twelve days after admission, the circulatory measurements were: arterial pressure, 120 systolic and 90 diastolic; venous pressure, 9.5 cm. of blood; circulation time, 13.5 seconds; volume of circulating blood, 94 cc. per kilogram of body weight.

At this time, it could be seen that the cervical veins were much better filled than on admission, and swelled further during pressure on the right upper quadrant. Reference to the figures cited shows that as the patient came out of shock the venous pressure mounted parallel to a rise in arterial pressure and an acceleration in the velocity of blood flow. Indeed, the venous pressure of 9.5 cm. is somewhat above normal, and is indicative of myocardial weakness due to the infarction.

It is a common sequence of events to find the venous pressure low, under 4 cm., when the patient enters the hospital in the early stages of infarction with the clinical picture of shock, and then as the shock passes away to observe that with the appearance of such manifestations of heart failure as orthopnea or swelling of the liver, the venous pressure rises to levels above the normal.

However, there are also instances of myocardial infarction in which venous hypotension persists for weeks. In such patients, there is also persistence of other manifestations of shock. Usually, but not invariably, the precordial pain and its radiations continue at least intermittently throughout this stage, and fever, leukocytosis and the electrocardiographic findings testify to the parallel prolongation of the myocardial necrosis. This course of events was well illustrated in case 10.

In Patients with Previous Infarction or Heart Failure.—The effect of myocardial infarction on venous pressure is usually quite different in patients who have had previous episodes of myocardial infarction or who are already incapacitated by severe heart failure due to the underlying coronary arteriosclerosis. In them, fresh infarction is more often documented by high than by low venous pressure. Of forty-three such patients, eleven had subnormal venous pressure, while in sixteen the venous pressure was above the upper limit of normal. The cases with low venous pressure were those in which the clinical picture was entirely dominated by shock. On the other hand, the more frequent cases with normal or high venous pressure presented predominantly the symptoms and signs of heart failure. Venous hypertension is especially apt to develop in patients who have had severe episodes of infarction, even though these antecedent infarctions were marked by subnormal venous pressure. In such cases, fresh coronary thrombosis with myocardial infarction may be documented by a rise in venous pressure to 20 cm. (cases 18 and 20).

Two circumstances are especially apt to be accompanied by high venous pressure:

(*a*) The first is extensive implication of the septum by the infarct. The postmortem examination in our cases with venous pressure of 20 cm. or higher revealed extensive infarction of the septum. The three cases in which initial infarction was accompaned by high venous pressure were all instances of septal infarction. However, even massive infarction of the septum is not invariably manifested by a rise in venous pressure. In several of our cases infarction of the septum was accompanied by low venous tension; the depressing effect of the shock on the venous pressure outweighed that of the cardiac weakness.

(*b*) The second circumstance causing rise in venous pressure is certain disturbances in rhythm resulting from infarction, notably auricular

fibrillation, nodal rhythm, heart block or ventricular tachycardia. All these were exemplified in our series. But it should be borne in mind that these arrhythmias, except perhaps ventricular tachycardia, are especially apt to occur on the basis of septal infarction, which is per se apt to raise the venous pressure. But the arrhythmia will tend to elevate the venous tension to the extent that it impairs the functional capacity of the right side of the heart.

However, the depressing effect of such changes in rhythm on the functional capacity of the heart does not always suffice to overcome the effect of the shock, which is generally pronounced in these cases, and we have encountered low venous pressure during ventricular tachycardia due to myocardial infarction.

CIRCULATION TIME

The circulation time was measured in thirty-eight patients, in most on repeated occasions. The initial measurements afforded the results shown in table three.

TABLE 3.—*Circulation Time in Myocardial Infarction*

Circulation Time, Seconds	Cases	Deaths
Less than 16¾ (normal)	9	1
17 to 19¾	6	0
20 to 29¾	9	2
30 to 39¾	8	5
40 or more	6	4

From the figures given in table 3 it is evident that in myocardial infarction the circulation time as estimated by the gluside method varies in different cases from normal values to very slow ones. How marked a retardation of the blood flow is represented by the slower rates given in the table will be clear if it is called to mind that a circulation time of forty seconds is about triple the mean normal.

There is no strict parallelism between the circulation time as estimated by the gluside method and the severity of the clinical picture of myocardial infarction. Despite severe and protracted pain, fever, leukocytosis, pericardial rub, gallop rhythm and the characteristic electrocardiographic changes of acute myocardial infarction, there may be comparatively little slowing of the blood flow as measured by the gluside method. Particularly significant is the fact that the patient may present the classic picture of shock and yet the circulation time by the gluside method reveals but slight, if any, slowing of the velocity of blood flow through the lungs. This is well illustrated in one of our cases.

CASE 5.—A man of 48 years was admitted because of constricting substernal pain of two days' duration. After several hours, a fever of 102 F. developed and he had chilly sensations. On admission, the patient's face had a grayish

pallor, while the lips and finger-nail beds were cyanotic, the hands and feet felt cold despite a rectal temperature of 102 F., and the skin was moist. He lay flat on one pillow without orthopnea or apparent dyspnea, breathing only twenty times per minute. The heart rate was 86, and a presystolic gallop rhythm was heard. Physical examination of the lungs revealed no abnormalities. The electrocardiogram revealed very low voltage, inversion of T_1 and T_2, and a slight elevation of the R T interval in the second lead. Circulatory measurements were: arterial pressure, 96 systolic and 54 diastolic; venous pressure, 2.5 cm. of blood; circulation time, twenty-one seconds, and volume of the circulating blood, 56 cc. per kilogram of body weight.

The patient thus presented the classic picture of circulatory shock due to myocardial infarction, with low venous and arterial pressures and subnormal volume of the circulating blood. That the arterial pressure was depressed was proved by the fact that ten months later it was 140 systolic and 80 diastolic. Nevertheless, despite all the evidence of severe impairment of the peripheral circulation, the circulation time as measured by the gluside method was only twenty-one seconds, representing a retardation of but slight degree.

A number of similar observations have revealed that in most instances in which the clinical picture of myocardial infarction is dominated by the phenomena of shock, the circulation time as estimated by the gluside method is but little prolonged. Indeed, in case 9, the circulation time was well within the limits of normal. Relatively slight prolongation of the circulation time occurs especially when the infarction is the first from which the patient has suffered and has not been preceded by a period of myocardial insufficiency due to arteriosclerotic disease of the heart. The explanation of the seeming incongruity between the only slightly retarded time as measured by gluside and the clinical picture of obvious and severe circulatory failure lies in the nature of the latter and of the method. It was mentioned previously that the gluside method (as well as other clinical methods for determining circulation time) is largely a measure of the pulmonary circulation time, i. e., of the velocity of blood flow through the lungs. In shock, as will be discussed later, the disturbance of blood flow is largely or exclusively in the periphery of the greater circulation; and it is this primarily peripheral disturbance that produces the coldness and cyanosis of the extremities and the low venous pressure. The comparatively slight prolongation of the time as estimated by the gluside method demonstrates the important fact that in cases of myocardial infarction with the clinical picture of shock, the peripheral circulatory disturbance is accompanied by little or no slowing of the blood flow through the lungs.

On the other hand, the circulation time as estimated by the gluside method is prolonged in cases of myocardial infarction which present such symptoms of heart failure as orthopnea, engorgement of the veins and swelling of the liver. Circulation time as slow as thirty or forty seconds, or even more, is common (tables 1 and 3). Prolongation of the circulation time is apt to be especially marked when the infarction has

been preceded by a period of cardiac insufficiency due to coronary arteriosclerosis, and often also hypertension. These patients generally have large hearts, testifying to the antecedent stage of heart failure. Examination also reveals evidence of pulmonary engorgement, and the prolongation of the circulation time is doubtless to be attributed almost entirely to the slowing of the blood flow through the lungs.

VOLUME OF CIRCULATING BLOOD

The volume of the circulating blood was determined in twenty-nine of the patients, in some on two occasions. Table 4 shows the results of the first measurements.

The fact that the volume of circulating blood varies within such wide limits in both directions—the lowest reading 49 cc. and the highest 127 cc. per kilogram of body weight—indicates that opposing influences come to play on this circulatory variable in myocardial infarction. One factor that we have been unable to gage is that of abnormality of the volume

TABLE 4.—*Volume of Circulating Blood in Myocardial Infarction*

Volume of Circulating Blood, CC. of Blood / Kg. Body Weight	Cases	Deaths
Less than 70	4	1
70 to 95 (normal)	11	5
More than 95	14	7

of the circulating blood prior to the infarction. In some instances of essential hypertension and of pulmonary emphysema, the volume is increased. As many of our patients had essential hypertension and some were moderately emphysematous, this factor must be taken into consideration in interpreting the volume of blood in rapid circulation. Myocardial infarction is not uncommon in polycythemia vera, but there was no evidence that any of our cases were of this variety.

Comparison of the volume of circulating blood with the rest of the clinical picture in myocardial infarction indicates that two opposing influences are of prime significance in determining the volume of blood in rapid circulation.

1. One of these is the presence of shock, which tends to be associated with a low volume of circulating blood. In initial attacks of myocardial infarction, in which the clinical picture is predominantly that of shock, the volume is subnormal or at the lower limit of the normal range. As the patient recovers from the shock, the volume rises. This was well illustrated in case 14. When the patient first entered the hospital in typical shock due to myocardial infarction, the volume of circulating blood was only 49 cc. per kilogram: ten days later, when the manifestations of shock had largely cleared up, the volume of circulating blood had risen to 73 cc.

2. In cases in which the picture is predominantly that of cardiac failure, the volume of circulating blood tends to be high. It is known that elevation in the volume is common in heart failure, being perhaps a compensatory mechanism. In accord with this, we found that a very high volume of circulating blood (127 cc. per kilogram in case 49 and 120 cc. in cases 57 and 58) occurred in patients who had had a protracted period of marked cardiac insufficiency prior to the infarction. Presumably, in such patients the elevation in volume persists and is even augmented after the acute phase of the myocardial infarction has been survived, if, as is usually the case, the heart continues to be inadequate. This we found to be true in several of our patients.

It is of special interest that in patients with antecedent heart failure, as well as in others with essential hypertension, infarction may be accompanied by an abnormally high volume of circulating blood, although the clinical features are those of shock. In such patients the venous pressure may be low despite the high volume (cases 49 and 33). These observations show that a subnormal volume of circulating blood is not an invariable characteristic of shock in myocardial infarction.

ARTERIAL PRESSURE

It has long been known that myocardial infarction most often results in a sharp drop in both systolic and diastolic pressure. Indeed, this is so characteristic that when a sudden fall in blood pressure accompanies the onset of circulatory failure in an arteriosclerotic or hypertensive person, the first suspicion entertained is that myocardial infarction has occurred.

The depressor effect of myocardial infarction was of course evident in our series. However, there are exceptional cases in which even elevated blood pressure remains at the previous level despite myocardial infarction with otherwise characteristic clinical features.

Two mechanisms come into consideration as primary pathogenetic factors in the drop in blood pressure accompanying myocardial infarction: (1) heart failure, i. e., decrease in the output of the left ventricle resulting from cardiac weakness and occurring despite adequate venous return to the heart, and (2) the peripheral circulatory failure of shock with consequent diminution in the venous return to the heart.

Comparison of the arterial pressure with the rest of the clinical picture indicates that the second of these mechanisms is generally the more important in causing the fall in arterial tension. In the instances of myocardial infarction in which the clinical features are predominantly those of cardiac insufficiency with intense pulmonary engorgement, the blood pressure tends to be maintained at a level relatively close to that prevailing prior to the infarction. Indeed, as has so often been observed by others under different circumstances, the blood pressure may actually

rise for a time when failure of the left ventricle is severe enough to produce outspoken pulmonary edema. Presumably, this is largely a consequence of asphyxia, being accompanied by intense cyanosis and dyspnea.

On the other hand, the fall in blood pressure is usually pronounced in the episodes of myocardial infarction which are marked by shock and in which the low venous pressure testifies to the deficient venous return to the heart. In such patients, the arterial pressure tends to rise as the other manifestations of shock clear up. However, as is well known, the blood pressure often remains permanently at a lower level than before the infarction. This is presumably due to a persistence of at least part of the cardiac element in the depression of the blood pressure, and is especially apt to occur in cases in which aneurysm of the ventricle develops.

It seems, indeed, that the concomitant presence of shock explains the aforementioned fact that the arterial pressure in many instances of myocardial infarction falls much more than in cardiac insufficiency of other causation. When the heart fails in valvular disease, for example, the only factor tending to depress the arterial pressure is the diminished output of the heart. But physiologic experiments (Tigerstedt [10]) show that the arterial pressure is maintained at its previous level by means of peripheral vasoconstriction despite even considerable decrease in the minute volume of the heart. Apparently such a regulatory mechanism functions when the cardiac output is diminished in valvular disease, for the blood pressure rarely falls to any considerable extent, if at all, even though dyspnea, venous and hepatic engorgement and edema evince the insufficiency of the heart. But the situation is different in myocardial infarction with shock. Here, the damage to the heart is accompanied by a functional disturbance in the peripheral circulation, which interferes with regulatory vasoconstriction. Moreover, the peripheral circulatory failure results in diminution in the venous return to the heart, as revealed by the empty peripheral veins and low venous pressure which is so characteristic of the condition. This diminution in venous return to the heart must result in a corresponding decrease in the cardiac output which, in the absence of peripheral vasoconstriction, depresses the arterial pressure.

PERIPHERAL CIRCULATORY FAILURE (SHOCK)

In all our cases of massive myocardial infarction, shock has been at least a significant and often the outstanding feature of the clinical picture. The word "shock" is used in the familiar, strictly clinical sense. The circulatory manifestations of severe shock in myocardial infarction

10. Tigerstedt, R.: Physiologie des Kreislaufes, ed. 2, Berlin, W. de Gruyter & Co., 1922, vol. 3, p. 96.

are, briefly, the following: grayish acrocyanosis, often accompanied by mottling of the skin (cutis marmorata) of other parts, notably the abdomen; extremities which are cold in comparison to the rectal temperature, although the actual temperature may not seem low if there is fever; moist skin which generally feels clammy because of the relatively low temperature at the surface; superficial respiration which may or may not be rapid, but no orthopnea; collapsed superficial veins, and a pulse which is most often rapid, small and of low tension.

Obviously, this picture is fundamentally identical with the shock which is common following trauma, hemorrhage or the perforation of a viscus. It is also akin to the circulatory collapse of diabetic coma, the crises of Addison's disease and those of various infections, and as such is to be classified as belonging to what Atchley [11] aptly termed "medical shock."

It is characteristic of the circulatory failure of shock that it results from disturbances initiated in the periphery of the circulation and not primarily as a consequence of cardiac insufficiency. The nature of the underlying peripheral circulatory disturbances is largely obscure, and doubtless varies in different forms of shock. However, they have as a common consequence, as has long been maintained by Yandell Henderson,[12] a diminution in the venous return to the heart. This is so characteristic, and so diametrically opposed to the venous engorgement of heart failure, that the demonstration of a diminution in venous return to the heart can be taken as adequate evidence that a given instance of circulatory failure is of peripheral origin and not due to insufficiency of the heart.

In the patients with myocardial infarction presenting the clinical picture just described, the existence of peripheral circulatory failure with deficient venous return to the heart is immediately indicated by observation of the superficial veins of the extremities and neck. These appear collapsed and fill slowly when compressed or when the hand is lowered below the level of the heart. When venesection is attempted the blood drips slowly from even a large needle, and to remove any considerable quantity of blood takes a long time. More precise information is afforded by the direct measurements of venous pressure, described earlier, which show that the venous pressure is subnormal. This is all the more significant because it is present despite a severe lesion of the heart which of itself would tend to raise the venous pressure. We have also observed that pressure on the right upper quadrant, which immediately raises the venous pressure in persons with cardiac insufficiency,

11. Atchley, D.: Medical Shock, J. A. M. A. **95**:385 (Aug. 9) 1930.

12. Henderson, Y.: Volume of Circulation and Its Regulation by Venopressor Mechanism, J. A. M. A. **97**:1265 (Oct. 31) 1931.

has no such effect in patients with myocardial infarction and low venous pressure—a further indication of the poor filling of the large veins.

The observations made furnish no unequivocal evidence regarding the causation of the low venous pressure in myocardial infarction. The problem is really only one aspect of the fundamental question of the origin of circulatory shock in general, which is still *sub judice*. Investigations of recent years (Atchley [11]) have shown that diminution in the volume of circulating blood is an important factor in many forms of shock, and that therapeutic measures which increase the volume often have a salutary influence on shock. The measurements described earlier show that in myocardial infarction the volume of circulating blood tends to be lowered, and in some of the cases is much below normal. However, it was also mentioned that in other cases with the typical picture of shock, including low venous pressure, the volume is normal or above normal. It seems probable that in these patients, as a result of cardiac failure or in correlation with hypertension, the volume of circulating blood was even higher prior to the infarction. The possibility, therefore, must be borne in mind that in such cases there may be a relative decrease in the volume of circulating blood below that to which the capacity of the vessels has become adjusted. The mechanism of the fall in the volume of circulating blood remains to be elucidated. We found no constant abnormality in the hematocrit reading or in the red blood cell count, which shows that extravasation of the plasma, so important in other forms of shock, plays no considerable part in that of myocardial infarction. It is therefore to be presumed that the diminution in the volume of circulating blood is due to a redistribution of the blood, whereby a smaller fraction of the total volume of blood in the body remains in active circulation and a larger fraction is stagnated in dilated capillaries and perhaps within the blood depots, originally described by Barcroft,[13] where it is not reached by the dye injected and contributes little to the venous return to the heart.

How myocardial infarction leads to the disturbances in the peripheral circulation, one of the manifestations of which is a decrease in the volume of the circulating blood, is another question to which we are unable to give an adequate answer. A chemical mechanism, with liberation from the necrotic heart muscle of substances with histamine-like action, seems improbable, because the shock and low venous pressure may set in within a short period after the onset of the first symptoms, before actual necrosis could be considerable. A nervous mechanism would seem much more likely. That reflexes actually affect the peripheral circulation in

13. Barcroft, J., and others: Observations upon the Effect of Altitude on the Physiological Processes of the Human Body, Tr. Roy. Soc., London, s.B **211**:351, 1922.

14. This footnote was deleted by the author.

coronary occlusion was indicated by Condorelli,[15] who found that occlusion of the left coronary artery of a dog is followed immediately by a considerable fall in the aortic pressure, which rises as soon as the coronary clamp is released; but if he cut the vagus and sympathetic nerves on both sides, subsequent occlusion of the left coronary artery caused no notable depression of the aortic pressure until ventricular fibrillation set in. How such reflexes affecting the peripheral circulation are initiated in myocardial infarction is unknown. It is not the anginal pain that set the mechanism in operation, for shock may be severe in myocardial infarction in the absence of pain. Indeed, Libman [16] found that shock is apt to be especially pronounced when myocardial infarction affects hyposensitive persons who do not complain of pain.

HEART FAILURE IN MYOCARDIAL INFARCTION

In other patients with myocardial infarction, usually those with a history of severe heart failure or prior infarctions, the symptoms are largely those of cardiac insufficiency. Evidence of failure of the left ventricle with pulmonary engorgement is always present, sometimes alone and sometimes combined with insufficiency of the right side of the heart, as manifested by a rise in the venous pressure and swelling of the liver. Peripheral edema, however, is unusual; it was present in but five of our fifty-nine cases. The circumstances under which failure of the right side of the heart was observed have already been discussed in conjunction with high venous pressure. In the cases showing the clinical picture of heart failure, the circulation time was prolonged and the volume of circulating blood increased.

Isolated failure of the left side of the heart is not infrequent in myocardial infarction. Most often, it is due to anterior infarction of the heart consequent on thrombosis of a branch of the left coronary artery. However, it may also result from posterior infarction in right coronary occlusion. The outstanding circulatory symptoms are dyspnea and orthopnea with evidence of pulmonary engorgement and accentuation of the second sound at the pulmonic area. The venous pressure is not elevated, and the liver is not enlarged. The pulmonary circulation time is prolonged, usually strikingly so. Episodes of paroxysmal nocturnal dyspnea are common. We have seen such banal symptoms of failure of the left ventricle in hypertensive and arteriosclerotic subjects, in whom only the electrocardiogram revealed that recent infarction was responsible. The extreme form of failure of the left ventricle

15. Condorelli, L.: Die Ernährung des Herzens und die Folgen ihrer Störung, Dresden, Theodor Steinkopff, 1932, p. 67.

16. Libman, E.: Studies in Pain, Tr. A. Am. Physicians **34**:52, 1929.

in myocardial infarction is that in which massive pulmonary edema develops, which may lead to quick death.

Pletnew,[17] Kohan and Budin[18] and others thought that they were able to infer the site of coronary thrombosis from the type of heart failure present. They reported observations indicating that thrombosis of the left coronary artery with anterior infarction results in failure of the left ventricle with pulmonary engorgement and enlargement of the heart to the left. On the other hand, they found that thrombosis of the right coronary artery with posterior infarction is characterized by failure of the right side of the heart, with swelling of the veins and liver and enlargement of the heart to the right. We have not found such a differentiation feasible. Our necropsy observations revealed that either anterior or posterior infarction can cause isolated failure of the left ventricle or combined insufficiency of the left and right ventricle with engorgement of both the lungs and the systemic veins. And when shock dominates, the venous pressure is low in thrombosis of the right as well as of the left coronary artery. Because of these observations, it has not seemed that the type of circulatory failure present permits, of itself, the differentiation between right and left coronary occlusion. However, Libman[19] found that when the liver becomes greatly enlarged within a few hours after the onset of myocardial infarction, the right coronary artery is the one affected.

In those of our patients with severe failure of the right side of the heart and high venous pressure who came to necropsy, extensive infarction of the interventricular septum was present. Such septal infarction may be due to thrombosis of either the right or the left coronary artery. Whether high venous pressure in coronary thrombosis is always due to septal infarction must be studied on more extensive material. However, it must be emphasized that even with extensive septal infarction the venous pressure in coronary thrombosis is low if shock dominates the clinical picture.

INTERRELATIONS OF SHOCK AND HEART FAILURE

The foregoing observations indicate that in myocardial infarction two distinct mechanisms operate to derange the circulation: (1) cardiac insufficiency, which tends to produce engorgement and a rise in pressure in the pulmonary circuit and in the systemic veins, and (2) shock, which

17. Pletnew, D.: Zur Frage der intravitalen Differentialdiagnose der rechten und linken Coronarthrombose des Herzens, Ztschr. f. klin. Med. **102**:295, 1925.

18. Kohan, B. A., and Budin, E. I.: Zur Frage der Differentialdiagnose der rechten und der linken Koronararterie des Herzens am Lebenden, Ztschr. f. Kreislaufforsch. **20**:199 (April 1) 1928.

19. Libman, E.: Some Observations on Thrombosis of the Coronary Arteries, Tr. A. Am. Physicians **34**:138, 1919.

diminishes the venous return to the heart and thereby tends to deplete and lower the pressure in the pulmonary circuit and great veins.

As regards the minute volume of the heart, both these derangements are synergistic, each tending to diminish the cardiac output. On the other hand, the two derangements are antagonistic in their effect on the venous pressure, heart failure tending to raise it and shock to lower it. The observation of the veins and the measurement of the venous pressure thus furnish a valuable index of the relative significance of shock and of cardiac insufficiency in producing circulatory failure in a patient with myocardial infarction. That this is a point with important therapeutic implications is evident.

As indicated in the section on venous pressure, the clinical picture of initial myocardial infarction is most often predominantly that of shock. Indeed, symptoms of heart failure may be entirely lacking despite clinical and electrocardiographic evidence of extensive infarction. The explanation of this remarkable phenomenon would seem to be that the presence of shock militates against the development of heart failure through the following mechanisms:

1. Symptoms of heart failure appear when the work which the heart is called on to perform exceeds the functional capacity of a chamber, so that it fails to empty as completely as before, and engorgement develops up-stream to the insufficient chamber. The work of the heart is a function of the volume of blood it is called on to pump (i. e., the venous return) and the resistance against which the blood has to be pumped (i. e., the pulmonary and aortic arterial pressures). In shock, both these factors are subnormal, for the venous return to the heart is decreased and the arterial pressure is depressed.

2. The decrease in the work of the heart due to shock in myocardial infarction may be so great that even the severely damaged heart is able to pump the smaller volume of blood that returns to it against the lowered aortic pressure. In such cases the circulatory status is that of shock, and evidence of heart failure is absent. In other instances, on the contrary, the diminution in the work of the heart is not sufficient to bring it within the functional capacity of the infarcted organ. In this event, orthopnea, signs of pulmonary engorgement, high venous pressure, swelling of the liver or other signs of heart failure develop. But even in such instances, the concomitant presence of primarily peripheral disturbances in circulation is often indicated by such manifestations as coldness and cyanosis of the hands disproportionate to the other evidences of heart failure, moisture of the skin and cutis marmorata.

A not uncommon sequence of events is the following: In the first days after the infarction, the clinical picture is that of shock with low venous pressure. Subsequently, most often between the second and

tenth days, the shock clears up and evidences of heart failure appear in the form of orthopnea and signs of pulmonary engorgement, with an accompanying rise in venous pressure. It is at this period that evidences of bronchopneumonia most often appear; they are perhaps correlated with the increasing pulmonary engorgement as the venous return to the heart increases before the left ventricle has recuperated sufficiently to master it.

In a real sense, then, shock operates as a protective mechanism for the heart in myocardial infarction. Of course, it is protection bought at a high price, for some patients succumb with the typical manifestations of shock. And the decreased cardiac output with low aortic pressure presumably lessens the coronary flow, which may be concerned in the production of ventricular fibrillation. But in other cases it may be presumed that the heart would not be able to carry on its function were it not for the decreased cardiac work due to shock. Moreover, the diminished work of the heart in shock must be accompanied by lower maximum intraventricular tension, and this may be an important reason why rupture of the heart occurs in only a small minority of instances of even extensive myocardial infarction. It is probably also the explanation of the fact that enlargement of the heart over its antecedent dimensions is most often not demonstrable in the first days of myocardial infarction.

In our cases of myocardial infarction, the immediate prognosis has been statistically much better when the clinical picture was that of shock with low venous pressure than when there was heart failure with high venous pressure. Of nineteen patients with venous pressure below 4 cm. on admission, five died. On the other hand, of nineteen patients who entered the hospital with venous pressure above normal, fifteen died. Of course, this difference is probably largely correlated with the fact, brought out previously, that low venous pressure is more common in initial infarction, while high venous pressure usually occurs in those with previous severe functional impairment of the heart. For the same reason, the prognosis is statistically much worse when the circulation time is greatly retarded (table 3).

THERAPY

It is not our purpose to discuss therapy. However, it may be pointed out that in myocardial infarction with shock and low venous pressure, as the patient at the time is not suffering from cardiac insufficiency, there would seem to be no indication for digitalis. Presumably, the general ill-repute of digitalis in myocardial infarction originated in its lack of beneficial effect in such cases. Venesection is also out of place, and is rendered difficult by the low pressure in the superficial veins. On the other hand, venesection and digitalis may be of great service in cases in which there is heart failure with pulmonary and venous engorgement.

The value of digitalis for such patients is often demonstrated objectively by the rapid fall in venous pressure to normal levels following digitalization. However, it should be borne in mind that, at least theoretically, digitalis predisposes to certain dangers in myocardial infarction. Notable among these are ventricular fibrillation as a result of greater irritability of the heart muscle, rupture of the heart or embolization of intraventricular thrombi in consequence of a more powerful systole, and possible deleterious effects of the coronary constriction as demonstrated by Gilbert and Fenn.[20] Whether these dangers are actual can be established only by observation of a larger series of cases. In any event, it seems obvious that the type of circulatory failure present should be taken into account in the treatment of myocardial infarction.

SUMMARY

Fifty-nine patients with recent myocardial infarction were studied from the point of view of circulatory dynamics. The venous pressure was measured in all, the circulation time in thirty-eight and the volume of circulating blood in twenty-nine of the subjects.

Two distinct mechanisms participate in the derangement of the circulation in myocardial infarction: (*a*) shock, or peripheral circulatory failure, which diminishes the venous return to the heart and tends to lower the pressure in the large systemic veins, and (*b*) heart failure, which tends to engorge the pulmonary circuit in consequence of insufficiency of the left side of the heart and to raise the systemic venous pressure in proportion to the insufficiency of the right side of the heart.

In initial myocardial infarction in persons without previous severe heart failure, the clinical picture is most often predominantly that of shock. The venous pressure is then subnormal. The blood flow through the lungs is slowed but little, if at all. The volume of circulating blood tends to be diminished.

When infarction affects patients with previous heart failure, the manifestations of either shock or cardiac insufficiency may be predominant. When heart failure dominates, the venous pressure is elevated or normal, the flow of blood through the lungs is retarded, and the volume of circulating blood is increased.

The diminished venous return due to shock lessens the work of the heart and thus militates against the development of cardiac insufficiency. It is because of this diminution in the venous return to the heart that engorgement of the lungs and systemic veins may be absent despite extensive myocardial infarction.

20. Gilbert, N. C., and Fenn, G. K.: The Effect of Digitalis on Coronary Flow, Arch. Int. Med. **50**:668 (Nov.) 1932.

The fall in arterial pressure is due not only to the weakness of the left ventricle but also to the peripheral circulatory failure of shock. Apparently the latter is usually the more important of the two factors. It is because of the concomitant presence of shock that a fall in the arterial pressure is so much more prominent in myocardial infarction than in other lesions of the heart.

Statistically, the immediate prognosis of myocardial infarction is better with low than with high venous pressure.

The type of circulatory failure present is of significance for the rational treatment of patients with myocardial infarction.

News and Comment

INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY

The First Congress of Gastro-Enterology will be held at Brussels, Belgium, Aug. 8 to 10, 1935. The secretary-general of the Congress is Dr. George Brohee, Rue de la Concorde, 64, Brussels. Dr. Max Einhorn, 20 East 63rd Street, New York, has been asked to form, and to act as chairman of, the North American Committee, and Dr. De Witt Stetten to serve as secretary of the committee.

Book Reviews

A Textbook of Bacteriology. By Hans Zinsser, Professor of Bacteriology and Immunology, Harvard University Medical School, and Stanhope Bayne-Jones, Professor of Bacteriology, Yale University Medical School. Price, $8. Pp. 1,226, with 174 illustrations. New York: D. Appleton-Century Company, 1934.

In 1910, Philip H. Hiss Jr. and Hans Zinsser published the first edition of their textbook of bacteriology. As they stated, the book was primarily a treatise on the fundamental laws and technic of this science; it was written in the hope of meeting the bacteriologic needs of medical students and also to interest practitioners in a fascinating subject. The book at once became recognized all over the world and soon earned a well deserved popularity, so that subsequent editions were published in 1914, 1916, 1918, 1922, 1927 and 1934.

The 1934 edition lives up to the standards of its predecessors: It brings the subject matter up to date; it is easily readable, being written in delightfully clear and succinct English, and it is printed in type comfortable to the eye and is well illustrated. At the end of each chapter are a few good references to the topics under discussion, thus prompting even the most casual student to further knowledge, and at the end of the book is an excellent index.

Bacteriology appears to be an extraordinarily alive subject. The second edition of this textbook, published twenty years ago, described adequately current knowledge of the subject. A volume nearly twice as large is necessary to accomplish the same purpose today. As one compares the second edition with the seventh, one is struck with the pertinency of what the authors remark in their preface to the latest edition. Certainly, the last few years have been eventful ones in bacteriology, and some of the newer knowledge has been revolutionary in its effect on old theories. The book is so written as to take due cognizance of this. It also lays more emphasis than heretofore on the diseases caused by Rickettsia and on the ultramicroscopic virus agents.

On the whole, this textbook deserves highest praise. Without doubt, it will fulfil the purpose for which it was written and will prove useful to bacteriologists, physicians and all those who are engaged in the investigation, management and prevention of infectious disease.

The Lyophilic Colloids (Their Theory and Practice). By Martin H. Fischer and Marian O. Hooker. Price, $4.50. Pp. 246, with 84 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1933.

This volume is a résumé of the work done by these two capable scientists during the last ten years not only in developing their concept of the physical state of matter (protoplasm) but also in studying the physical and chemical laws which make this concept probable. By studying the physical and physicochemical properties of such colloidal systems as phenol/water, quinoline/water and casein/water (to mention a few), they arrived at the conclusion that protoplasm itself is not a solution of protein and minerals in water, but that it is actually one of the inverse type. In other words, instead of being a dilute solution of "x" in water, it is a concentrated solution of water in "x," and as such cannot possibly fit into the schemata proposed by the "dilute solution" chemists. As a corollary to the axiom may be mentioned new and extremely interesting information regarding the disenfranchisement of the cell membrane and the osmotic theory, as well as the proposal of new explanations for such phenomena as the absorption of water; edema; the relation of electrolytes, protein and water in the cell; acidosis and alkalosis, and, finally, synthesis within the cell itself.

The physician will be most interested in the third portion of the book, which deals with biologic applications, but in order to attain properly the authors' point of view it is necessary to read carefully part one, which reveals the general nature of the lyophilic colloid. Part two, on chemical applications, will not prove of much interest to students of medical science.

The volume is clearly written, and the arguments are logically presented, but a more orderly arrangement of the many illustrations and graphs with reference to the context would not be amiss. It might be added that the reader who has no previous knowledge of the colloidal state will probably find himself somewhat handicapped in attempting an intelligent and complete understanding of the work.

Traité de physiologie normale et pathologique. Tome V. **Respiration.** Published under the direction of G. H. Roger and Léon Binet. Price, 80 francs, stitched; 100 francs, bound. Pp. 474, with 147 figures and 3 colored plates. Paris: Masson & Cie, 1934.

This volume is the fifth of a work of eleven volumes on normal and pathologic physiology. A general preface points out that a treatise of this sort, while emphasizing the value of facts in the development of the present position of a science, should also point out the imperfections and the unfinished nature of the knowledge.

The work purports, in spite of its size, to be merely elementary, treating only of what is indispensable to a solid foundation of pathology.

The subdivisions of the subject "Respiration" have, as in the other volumes of the work, been written by various authors, as follows: "The General Principles of Tissue Respiration," by P. Thomas; "The Histophysiology and Biochemistry of the Lungs, and Pulmonary Ventilation" (mechanics, pulmonary circulation, comparative physiology and the pleura, by L. Binet; a long and interesting chapter, "Gaseous Exchange," by L. Dautrebande; "The Internal Functions of the Lungs, Exclusive of Gaseous Exchange" (the influence on blood fat, cholesterol, lecithin, antitoxic action, coagulation of the blood, etc.), also by L. Binet, and a chapter "Basal Metabolism" by H. Hermann. Another particularly interesting chapter is "The Nervous Control of Respiration," by C. Heymans, who is preeminently capable of discussing this matter. Binet has also written a chapter "Abnormal Breathing" (asphyxia, mountain sickness, excess of oxygen, oxygen and carbon dioxide treatment of asphyxia, artificial respiration, drugs stimulating the respiratory center and other phases of the subject).

The work is a credit to the French and Belgian authors who have collaborated in producing this volume. The foreign modern literature is well represented in the references.

Médecine et éducation. By Drs. G. Mouriquand, M. Péhu, P. Bertoye, J. Barbier, P. Vignard, P. Mazel and P. D'Espiney, Father R. P. Charmot and Abbot J. Monchanin. Price, 15 francs, 50 centimes. Pp. 224. Lyon: Lavandier, 1934.

In Lyon a group of doctors, philosophers and biologists have evidently grouped together to study various complexities of human life. The first volume of their publications dealt with matters pertaining to sex, the second with heredity and the third with the importance of rhythm to life. The fourth was entitled "Formes, vie et pensée." The present volume deals with education.

This volume is a compilation of essays by the various authors of the book, showing in general that for the benefit of posterity the physician must play an increasingly important part in the process of education and must bring to bear the light of his special knowledge on the problems which perplex school teachers. Each chapter is interestingly written, beginning with an introductory appeal to educators for the collaboration of physicians by Father Charmot and ending with a concluding chapter on the ideals of education by Abbot Monchanin. The body

of the book is written by a group of physicians who discuss such topics as the physical and mental development of children, conditional reflexes and their rôle in education, the importance of adequate physical education to mental development, sex education and methods of handling nervous children or children with antisocial tendencies.

The book is an unusual one and should prove stimulating to physicians in this country who are school physicians or who are concerned with the management of young patients. On the whole, it is worth reading.

Die klinische Röntgendiagnostik der inneren Erkrankungen. By Dr. Herbert Assmann. Fifth edition. Price, 87 marks. Pp. 1248. Berlin: F. C. W. Vogel, 1934.

Assmann's book, which is familiar to every radiologist and internist, may now be said to have become a classic; "monumental" is the only adjective which adequately describes this vast compendium. The reviewer obviously can single out only a few points for comment. First, the general get-up—paper, printing and arrangement—is excellent and of a sort appropriate for a durable book; the work is conveniently divided into two volumes. Next should be mentioned the diagrams and reproductions of roentgenograms, more than 1,200 in number, illustrating every phase of the subject. Not only are these illustrations well selected, but the technical reproduction is excellent. The text, on the whole, is sound and is clearly written by one familiar with both the roentgenologic and clinical aspects of internal diseases. Reports of individual cases of typical, rare and interesting conditions make it possible for the physician to orient himself on practically any problem which he may encounter. That the revision is up to date is shown by the inclusion of such topics as arteriography. The bibliographies appended to each section are comprehensive, and there is an index. A particularly useful feature is the discussion of the normal roentgenologic appearances of the various organs—the heart, gastrointestinal tract and others.

Clinical Miscellany: The Mary Imogene Bassett Hospital, Cooperstown, N. Y. Volume I. By several contributors. Price, $3. Pp. 206, with 15 illustrations, 25 charts and graphs and index. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

Twenty-two articles by eight members of the hospital staff on a "collection of selected clinical observations with interpretative comments" representing "an effort to activate fragments of experience" comprise the volume. Each case is clearly presented and has been thoroughly studied. Most commendable is the scientific curiosity evidenced in the "interpretative comments."

With the literature so crowded and with such easy access to standard medical publications, one questions the advisability of publishing such a collection, apparently the first of a series of which this is volume 1. The book is printed on good paper and is well bound, and the illustrations are excellent.

Handbook of Therapeutics. By David Campbell. Second edition. Price, $4.75. Pp. 444, with 72 figures and 9 tables. Baltimore, William Wood & Company, 1934.

This little book gives in fairly adequate form the treatment of internal disease. Like all brief compendia it suffers in places from undue abbreviation, as well as from the inclusion of some material which is relatively useless, such as brief remarks on climatotherapy, spas, etc. The point of view, on the whole, seems sound, with some glaring lapses, for example, the suggestion that a few brief courses of therapy intermittently given suffice in the early stages of syphilis. A great many statements, such as the dietary prescriptions for Bright's disease, do not seem to rest on any rational basis. On the whole, the book is satisfactory, but a really adequate brief outline of therapy remains to be written.

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